



DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF INSPECTOR GENERAL

WASHINGTON, DC 20201



SEP 18 2020

Nick Lagunowich
Regional President North America,
Rare Disease
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Re: OIG Advisory Opinion No. 20-05

Dear Mr. Lagunowich:

We are writing in response to your request for an advisory opinion regarding a pharmaceutical manufacturer's proposal to provide cost-sharing assistance directly to Medicare beneficiaries who are prescribed either of two formulations of its drug (the "Proposed Arrangement"). Specifically, you have inquired whether the Proposed Arrangement would constitute grounds for the imposition of sanctions under the civil monetary penalty provision prohibiting inducements to beneficiaries, section 1128A(a)(5) of the Social Security Act (the "Act"), or under the exclusion authority at section 1128(b)(7) of the Act, or the civil monetary penalty provision at section 1128A(a)(7) of the Act, as those sections relate to the commission of acts described in section 1128B(b) of the Act, the Federal anti-kickback statute.

You have certified that all of the information provided in your request, including all supplemental submissions, is true and correct and constitutes a complete description of the relevant facts and agreements among the parties.

In issuing this opinion, we have relied on the facts and information presented to us and, in accordance with 42 C.F.R. § 1008.39(d), other publicly available information. We have not undertaken an independent investigation of the certified facts and information presented to us by Pfizer Inc., the requestor of this opinion. This opinion is limited to the facts presented to us by Pfizer Inc. and other publicly available information found in the course of our independent inquiry in connection with our assessment of the Proposed Arrangement.

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Based on the facts certified in your request for an advisory opinion, supplemental submissions, and other publicly available information, we conclude that: (i) the Proposed Arrangement, as structured, would not generate prohibited remuneration under the civil monetary penalty provision prohibiting inducements to beneficiaries, section 1128A(a)(5) of the Act; and (ii) the Proposed Arrangement would generate prohibited remuneration under the anti-kickback statute if the requisite intent to induce or reward referrals for, or purchases of, items and services reimbursable by a Federal health care program were present and that the Office of Inspector General (“OIG”) could potentially impose administrative sanctions on Pfizer Inc. under sections 1128(b)(7) or 1128A(a)(7) of the Act (as those sections relate to the commission of acts described in section 1128B(b) of the Act) in connection with the Proposed Arrangement. Any definitive conclusion regarding the existence of an anti-kickback statute violation requires consideration of all of the facts and circumstances of the arrangement as implemented, including a party’s intent.¹ Where, as is the case here, the arrangement is proposed but has not yet been implemented, we cannot reach a definitive conclusion regarding the existence of an anti-kickback statute violation.

This opinion may not be relied on by any persons other than Pfizer Inc., the requestor of this opinion, and is further qualified as set out in Part IV below and in 42 C.F.R. Part 1008.

I. FACTUAL BACKGROUND

A. The Disease and Available Treatment Options

Transthyretin amyloid cardiomyopathy (“ATTR-CM” or the “Disease”) is a progressive, rare disease caused by deposition of transthyretin amyloid fibrils in the heart that can lead to heart failure and death.² The Disease can be an inherited condition, known as the hereditary form, or it can occur spontaneously, known as the wild-type form. Pfizer Inc.

¹ See accord OIG, Medicare and State Health Care Programs: Fraud and Abuse; Issuance of Advisory Opinions by the OIG, 62 Fed. Reg. 7,351–52 (Feb. 19, 1997), available at <https://oig.hhs.gov/authorities/docs/interim.pdf>.

² National Institutes of Health, Transthyretin Amyloidosis (2020), available at <https://ghr.nlm.nih.gov/condition/transthyretin-amylidosis#genes>; see also Ronald M. Witteles et al., Screening for Transthyretin Amyloid Cardiomyopathy in Everyday Practice, JACC: Heart Failure, vol. 7 (Aug. 2019), available at <https://heartfailure.onlinejacc.org/content/7/8/709>.

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(“Requestor”), a pharmaceutical manufacturer, estimated that approximately 100,000 to 150,000 Americans are affected by the Disease.³

Requestor manufactures and markets two forms of tafamidis, Vyndaqel® and Vyndamax® (each, a “Medication” and collectively, the “Medications”). In 2019, the U.S. Food and Drug Administration (“FDA”) approved the Medications for the treatment of both the wild-type and the hereditary forms of the Disease in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.⁴ Requestor certified that the majority of patients with the Disease are Medicare beneficiaries, and the majority of patients who may be prescribed the Medications will be Medicare beneficiaries. According to Requestor, the Medications are not curative. However, a multicenter, international, double-blind, placebo-controlled phase 3 trial found that one form of the Medications reduced all-cause mortality and the frequency of cardiovascular-related hospitalizations and also reduced decline in functional capacity and quality of life.⁵

With respect to alternative treatments for the Disease, Requestor certified that there may be non-pharmacological treatments (e.g., a heart transplant or dual heart and liver transplant); while such transplants have had some success, Requestor certified that they have limited application because most patients with the Disease are too sick and have too

³ Requestor certified that its prevalence estimate of the Disease is based on information available to Requestor and that such estimate may change over time as knowledge of the Disease improves.

⁴ Prior to its approval of the Medications, the FDA had not approved a pharmacological therapy to treat the Disease. According to Requestor, it does not expect FDA approval for a competitor therapy until 2021 or later. Requestor further certified that some patients who could not afford their cost-sharing obligations for the Medications elected to enroll in a phase 3, placebo-controlled, clinical trial for a drug of another manufacturer that is being studied for the treatment of the Disease. Requestor asserted that, even if the FDA were to approve another therapy for the treatment of the Disease, “if the Medications demonstrate superior efficacy and safety” then that superior efficacy and safety would be relevant to the fraud and abuse analysis of the Proposed Arrangement in the same way that the lack of FDA-approved alternatives is now.

⁵ Mathew S. Maurer et al., Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy, N Engl J. Med. 2018; 379:1007–16 (Sept. 13, 2018), available at <https://www.nejm.org/doi/pdf/10.1056/NEJMoa1805689?articleTools=true>.

many comorbidities to meet transplant criteria. In addition, according to Requestor, some physicians prescribe Onpattro® and Tegsedi® off-label for treatment of the Disease.⁶

Requestor set the list price at \$225,000 for each one-year course of treatment with the Medications. According to Requestor, at this price and based on cost-sharing requirements in the phases of the standard Medicare Part D benefit (*i.e.*, deductible, initial coverage, coverage gap, catastrophic), a Medicare beneficiary enrolled in the standard benefit must pay annually approximately \$13,000 in out-of-pocket expenditures for the Medications. According to Requestor, a significant portion of Medicare beneficiaries cannot afford to purchase the Medications because of these annual out-of-pocket expenses; stated another way by Requestor, these out-of-pocket costs operate as a financial impediment for a substantial portion of the Medicare population, preventing them from purchasing the Medications. Requestor certified that, in 2019, many Medicare beneficiaries filling their first order for the Medications would face \$5,100 in true out-of-pocket (“TrOOP”) spending, and therefore would reach the catastrophic phase (which had a threshold of \$5,100 in 2019) with their first prescription.⁷ Requestor also certified that, once beneficiaries are in the catastrophic coverage phase, the coinsurance requirement in that phase would be prohibitive for many beneficiaries.⁸

⁶ According to Requestor, “some physicians have prescribed off-label a drug that is not approved to treat [the Disease] . . . because that other drug is covered under Medicare Part B, for which Medigap insurance is available to reduce the patient’s out-of-pocket expenses.” Requestor further certified that, “[t]here is no question that some physicians may consider drug costs and a patient’s out-of-pocket burden when making prescribing judgments.”

⁷ In the catastrophic phase of the Part D benefit, the Medicare program pays 80 percent of the costs for pharmacological therapies through reinsurance; the plan pays 15 percent of these costs; and the beneficiary is responsible for coinsurance equal to the greater of (i) 5 percent of the costs of therapies such as the Medications or (ii) \$3.60 for generic drugs and \$8.95 for brand-name drugs in 2020. See Medicare Payment Advisory Commission, Report to the Congress: Medicare and the Health Care Delivery System (June 2020), available at http://www.medpac.gov/docs/default-source/reports/jun20_reporttocongress_sec.pdf?sfvrsn=0; see also Kaiser Family Foundation, An Overview of the Medicare Part D Prescription Drug Benefit (Nov. 2019), available at <https://www.kff.org/medicare/fact-sheet/an-overview-of-the-medicare-part-d-prescription-drug-benefit/>.

⁸ Underscoring the significance of ability-to-pay as an impediment to purchasing the Medications, Requestor stated, “offering co-payment assistance to help eligible patients afford a clinically-appropriate medication, when such medication is the only approved medication for the disease and the principal reason that patients would not fill their

B. The Proposed Arrangement

1. The Subsidy Program

Requestor certified that it has designed an assistance program to address the financial impediment of the out-of-pocket costs for the Medications. Specifically, under the Proposed Arrangement, Requestor would institute a cost-sharing assistance program specific to Medicare beneficiaries who are prescribed the Medications (the “Subsidy Program”). To be eligible for financial assistance under the Subsidy Program, the applicant must: (i) be a Medicare beneficiary enrolled in either a Part D plan or a Medicare Advantage – Part D (“MA-PD”) plan that covers the Medications; (ii) be a United States resident; (iii) meet the Subsidy Program’s criteria for financial need, which Requestor would set as a household income between 500 percent and 800 percent of the Federal Poverty Level (“FPL”); and (iv) have been prescribed one of the Medications on-label for the treatment of the Disease. Requestor certified that Medicare beneficiaries with household incomes up to 500 percent of the FPL would continue to be eligible for Requestor’s existing free drug program for the Medications, except that Requestor has required, and would continue to require, that patients not be able to receive assistance from other funding sources, including the Medicare Low-Income Subsidy,⁹ in order to be eligible for Requestor’s free drug program.

Requestor certified that it would not offer assistance under the Subsidy Program as part of any advertisement or solicitation for the Medications. According to Requestor, if a beneficiary qualifies for the Subsidy Program, Requestor, through a third-party Subsidy Program administration vendor,¹⁰ would complete enrollment by activating a physical card, issuing a personal identification number to the beneficiary, or both (collectively, the

prescriptions is the inability to pay their out-of-pocket costs, does not improperly induce the underlying prescribing decisions” (emphasis added).

⁹ The Medicare Low-Income Subsidy provides premium and cost-sharing assistance for beneficiaries with household incomes up to 150 percent of the FPL. According to publicly available data, as of March 2020, approximately 27.2 percent of Medicare beneficiaries enrolled in Medicare Part D receive a full or partial subsidy from the Federal government as part of the Medicare Low-Income Subsidy. See Centers for Medicare and Medicaid Services, LIS Enrollment by Plan (Mar. 2020), available at <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/MCRAdvPartDEnrolData/LIS-Enrollment-by-Plan>. Counts and percentages are calculated based on plan enrollments greater than 10.

¹⁰ We have not been asked to opine on, and express no opinion regarding, the arrangement between Requestor and the third-party vendor.

“Subsidy Card”) that the beneficiary would use at the point of sale to receive cost-sharing assistance when purchasing the Medications. Under the Subsidy Program, a beneficiary would be responsible for a monthly copayment of up to \$35 at the point of sale each time he or she fills a prescription for one of the Medications. Requestor, through its vendor, would pay 100 percent of the beneficiary’s remaining cost-sharing obligations for the Medications, including any deductible and required cost sharing owed during the initial coverage phase, the coverage gap phase, and the catastrophic coverage phase.¹¹ Requestor certified that a beneficiary would be eligible to obtain a Subsidy Card regardless of which provider or practitioner prescribes the Medications.

Requestor certified that the Subsidy Program would provide assistance only for the Medications and would not provide financial support for other FDA-approved pharmacological therapies to treat the Disease or other medical needs of beneficiaries diagnosed with the Disease (e.g., prescription drugs used by the patient in connection with managing the Disease, treating symptoms of the Disease, or treating pain and other side effects of the Disease). Requestor also certified that certain foundations operating patient assistance programs presently have funds covering amyloidosis (of which the Disease is a type).

Based on publicly available data maintained by the Centers for Medicare and Medicaid Services, approximately 91 percent of Medicare beneficiaries have a household income below 800 percent of the FPL.¹² Of the beneficiaries comprising that 91 percent, based on facts certified by Requestor, those with incomes at or below 500 percent of the FPL would be eligible to receive assistance through either the Medicare Low-Income Subsidy or Requestor’s free drug program, and the balance (with household incomes between 500 percent and 800 percent of the FPL) would be eligible to receive cost-sharing assistance through the Subsidy Program. The remaining 9 percent of Medicare beneficiaries would not be eligible for assistance through the Subsidy Program, Requestor’s free drug program, or the Medicare Low-Income Subsidy.

¹¹ Requestor certified that the purpose of the Subsidy Program is “to provide copay assistance directly to eligible Medicare Part D beneficiaries to help them pay the TROOP costs required to matriculate through the Part D deductible, initial coverage phase and coverage gap and then to assist patients with affording the 5% coinsurance required during the catastrophic phase.”

¹² Centers for Medicare and Medicaid Services, Medicare Current Beneficiary Survey, Survey File data. Baltimore, MD: U.S. Department of Health and Human Services, 2018, available at <https://www.cms.gov/research-statistics-data-and-systemsresearchmcbscodebooks/2018-mcbs-survey-file>.

2. The Hub

Requestor has developed a patient support hub, VyndaLink (the “Hub”), that is operated by a third-party vendor pursuant to a written services agreement.¹³ The Hub would administer the Subsidy Program. Requestor certified that prescribing physicians would be able to contact the Hub to learn about the Subsidy Program.

Requestor certified that the Hub, which is already in place, currently uses the following enrollment process and would employ the process in the same manner for purposes of enrolling patients in the Subsidy Program. First, Requestor certified that, to enroll a patient in the Hub, both the prescriber and the patient must complete and sign a patient enrollment form. According to Requestor, the prescriber must provide prescription information and must confirm that he or she has prescribed the Medication for the treatment of the Disease. The prescriber also must certify that he or she has made an independent judgment that the Medication is medically necessary for the patient and that all information provided on the form is accurate. If the patient seeks financial assistance, the patient also must provide certain financial information and documentation of annual household income.

For purposes of the Subsidy Program, Requestor certified that, once a beneficiary is enrolled in the Hub, the Hub would conduct a benefits investigation to determine coverage for the Medication under the applicant’s Part D or MA-PD plan, including out-of-pocket costs and payor coverage requirements. If the beneficiary seeks financial assistance, the Hub first would conduct alternative funding research to determine if other options (e.g., the Medicare Low-Income Subsidy) are available to provide financial assistance to the beneficiary.

Requestor certified that the Hub would conduct an individualized, case-by-case income determination based on a uniform measure of financial need and would determine a beneficiary’s eligibility for the Subsidy Program in a verifiable, uniform, and consistent manner. Once the Hub verifies that a beneficiary is eligible for the Subsidy Program, it would enroll the beneficiary and would communicate such enrollment to the beneficiary, the prescriber (upon the prescriber’s request), and the applicable specialty pharmacy, as described in more detail below.

3. Dispensing Pharmacies

Requestor certified that eligible beneficiaries would be able to use the Subsidy Card at any specialty pharmacy that Requestor authorizes to dispense the Medications (a

¹³ We have not been asked to opine on, and express no opinion regarding, the services arrangement between Requestor and the Hub.

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“Dispensing Pharmacy”), and the Subsidy Card would not be conditioned on a beneficiary using a particular Dispensing Pharmacy.¹⁴ Likewise, according to Requestor, the Subsidy Program would not give preference to any particular Dispensing Pharmacy and is structured such that the beneficiary would have the same limited cost-sharing obligation (\$35 per monthly fill) regardless of the Dispensing Pharmacy he or she selects to fill the prescription for the Medications.

According to Requestor, Dispensing Pharmacies are the only pharmacies authorized by Requestor to dispense the Medications to any patient who wishes to purchase the Medications, regardless of whether the patient is eligible for the Subsidy Program. Prior to the commercial launch of the Medications, Requestor conducted a request for proposal (“RFP”) process inviting specialty pharmacies to submit information describing their qualifications to be a Dispensing Pharmacy. To be eligible to serve as a Dispensing Pharmacy, the specialty pharmacy must have met several criteria set forth by Requestor.

At the conclusion of the RFP process, Requestor selected a number of pharmacies that met its criteria. Requestor certified that no other specialty pharmacies have since requested to be a Dispensing Pharmacy. According to Requestor, if other specialty pharmacies were to ask Requestor to participate as a Dispensing Pharmacy, Requestor would evaluate their qualifications under the same criteria referenced above and would base its decision on whether to include the specialty pharmacy on: (i) the ability of the specialty pharmacy to meet the criteria and (ii) whether it is in the best interests of patients to include the additional specialty pharmacy.

Requestor further certified that regional specialty pharmacies that are owned or affiliated with institutions (*i.e.*, hospitals and integrated delivery networks) that: (i) have experience with the Disease, including diagnosing and managing patients diagnosed with the Disease, (ii) agree to contract with Requestor or Requestor’s agent and comply with all contract terms, and (iii) are able to meet certain basic data reporting requirements, are eligible to be a Dispensing Pharmacy. Requestor identified specialty pharmacies owned by or affiliated with institutions that met these requirements, and some of these specialty pharmacies chose to participate as a Dispensing Pharmacy.

Requestor certified that, to its knowledge, there has not been any instance where there were no Dispensing Pharmacies included among the preferred pharmacies in a beneficiary’s Medicare Part D or MA-PD plan. Requestor certified that if a beneficiary’s plan were to require the beneficiary to use a particular specialty pharmacy (“Plan Pharmacy”) and that Plan Pharmacy is a Dispensing Pharmacy, then the beneficiary would be able to use the Subsidy Card at that Plan Pharmacy. If a beneficiary’s plan were to allow the beneficiary to obtain the Medications at more than one Dispensing

¹⁴ Requestor certified that it does not own or operate, directly or indirectly, any pharmacies that dispense the Medications.

Pharmacy, the Hub would ask the beneficiary and the prescribing physician whether they have a preference. If neither the beneficiary nor the prescribing physician has a preference, the Hub would transfer the prescription to a Plan Pharmacy that is a Dispensing Pharmacy using an objective “round robin” process.

Notwithstanding the foregoing, Requestor certified that, if a Part D or MA-PD plan would otherwise require a beneficiary to use a Plan Pharmacy that is not a Dispensing Pharmacy, the Hub would send the prescription to the beneficiary’s or the prescribing physician’s preferred Dispensing Pharmacy. If neither the patient nor the prescribing physician expresses a preference, the Hub would send the prescription to the Dispensing Pharmacy with the lowest patient out-of-pocket costs (as determined by the Part D or MA-PD plan). If more than one Dispensing Pharmacy offers the patient lowest out-of-pocket costs or if the out-of-pocket costs are the same across all or many Dispensing Pharmacies, the Hub would send the prescription to one of the Dispensing Pharmacies offering the lowest out-of-pocket costs using an objective, “round robin” process. The recipient pharmacy would then address coverage and reimbursement issues with the beneficiary’s plan.

II. LEGAL ANALYSIS

A. Law

1. Federal Anti-Kickback Statute

The anti-kickback statute makes it a criminal offense to knowingly and willfully offer, pay, solicit, or receive any remuneration to induce or reward, among other things, referrals for, or purchases of, items or services reimbursable by a Federal health care program.¹⁵ Where remuneration is paid purposefully to induce or reward referrals or purchases of items or services payable by a Federal health care program, the anti-kickback statute is violated. By its terms, the statute ascribes criminal liability to parties on both sides of an impermissible transaction. For purposes of the anti-kickback statute, “remuneration” includes the transfer of anything of value, directly or indirectly, overtly or covertly, in cash or in kind.¹⁶

¹⁵ See section 1128B(b) of the Act.

¹⁶ As we have stated previously, “Congress’s intent in placing the term ‘remuneration’ in the statute in 1977 was to cover the transferring of anything of value in any form or manner whatsoever. The statute’s language makes clear that illegal payments are prohibited beyond merely ‘bribes,’ ‘kickbacks,’ and ‘rebates,’ which were the three terms used in the original 1972 statute.” OIG, Medicare and State Health Care Programs: Fraud

The statute has been interpreted to cover any arrangement where one purpose of the remuneration is to induce or reward referrals for items and services reimbursable by a Federal health care program.¹⁷ Violation of the statute constitutes a felony punishable by a maximum fine of \$100,000, imprisonment up to ten years, or both. Conviction will also lead to automatic exclusion from Federal health care programs, including Medicare and Medicaid. Where a party commits an act described in section 1128B(b) of the Act, the OIG may initiate administrative proceedings to impose civil monetary penalties on such party under section 1128A(a)(7) of the Act. The OIG may also initiate administrative proceedings to exclude such party from the Federal health care programs under section 1128(b)(7) of the Act.

Congress has developed several statutory exceptions to the Federal anti-kickback statute.¹⁸ In addition, the U.S. Department of Health and Human Services has promulgated safe harbor regulations that define practices that are not subject to sanctions under the anti-kickback statute, even though they potentially may be capable of inducing referrals of federally reimbursable business.¹⁹ The safe harbors set forth specific conditions that, if met, assure entities involved of not being prosecuted or sanctioned for the arrangement qualifying for the safe harbor. However, safe harbor protection is afforded only to those arrangements that precisely meet all of the conditions set forth in the safe harbor.

2. Beneficiary Inducements CMP

A separate section of the Act, section 1128A(a)(5) (the “Beneficiary Inducements CMP”), provides for the imposition of civil monetary penalties against any person who offers or transfers remuneration to a Medicare or State health care program (including Medicaid) beneficiary that the benefactor knows or should know is likely to influence the beneficiary’s selection of a particular provider, practitioner, or supplier for the order or receipt of any item or service for which payment may be made, in whole or in part, by Medicare or a State health care program (including Medicaid). The OIG may also initiate

and Abuse; OIG Anti-Kickback Provisions, 56 Fed. Reg. 35,952 (July 29, 1991), available at <https://oig.hhs.gov/fraud/docs/safeharborregulations/072991.htm>.

¹⁷ See, e.g., United States v. Nagelvoort, 856 F.3d 1117 (7th Cir. 2017); United States v. McClatchey, 217 F.3d 823 (10th Cir. 2000); United States v. Davis, 132 F.3d 1092 (5th Cir. 1998); United States v. Kats, 871 F.2d 105 (9th Cir. 1989); United States v. Greber, 760 F.2d 68 (3d Cir. 1985), cert. denied, 474 U.S. 988 (1985).

¹⁸ Section 1128B(b)(3) of the Act.

¹⁹ See 42 C.F.R. § 1001.952.

administrative proceedings to exclude such party from the Federal health care programs. The Beneficiary Inducements CMP “is a separate and distinct authority, completely independent of the [Federal] anti-kickback statute.”²⁰

A distinct definition of “remuneration” applies exclusively to section 1128A of the Act, which includes the Beneficiary Inducements CMP. Specifically, section 1128A(i)(6) of the Act defines “remuneration” to include “the waiver of coinsurance and deductible amounts (or any part thereof), and transfers of items or services for free or for other than fair market value.”²¹ Section 1128A(i)(6) of the Act also sets forth a number of exceptions to the definition of “remuneration” that apply for purposes of section 1128A of the Act. These exceptions protect certain remuneration from violating the Beneficiary Inducements CMP. These exceptions²² apply only for the purposes of the definition of “remuneration” applicable to section 1128A of the Act (the CMP statute); they do not apply for purposes of section 1128B(b) of the Act (the Federal anti-kickback statute).

B. Analysis

Under the Proposed Arrangement, Requestor seeks to provide cost-sharing subsidies directly to Medicare beneficiaries who purchase its Medications. As an initial matter, the OIG has been and continues to be extremely mindful of the importance of ensuring that beneficiaries who enroll in Medicare Part D have access to medically necessary drugs. We also recognize that, presently, there are no other FDA-approved pharmacological therapies for treatment of the Disease. Our prior guidance has contemplated this scenario; specifically, we have stated that we believe lawful avenues exist for pharmaceutical manufacturers and others to help ensure that all Part D beneficiaries can afford medically necessary drugs, including in those instances where there may be only

²⁰ OIG, Health Care Programs: Fraud and Abuse; Revised OIG Civil Money Penalties Resulting From the Health Insurance Portability and Accountability Act of 1996, 63 Fed. Reg. 14,393, 14,395 (Mar. 25, 1998), available at <https://www.govinfo.gov/content/pkg/FR-1998-03-25/pdf/FR-1998-03-25.pdf>.

²¹ See also 42 C.F.R. § 1003.110 (defining “remuneration,” for purposes of the regulations implementing the Beneficiary Inducements CMP, to be consistent with the definition of “remuneration” set forth at section 1128A(i)(6) of the Act).

²² See, e.g., section 1128A(i)(6)(E) of the Act (setting forth the exception for waivers of coinsurance and deductible amounts); section 1128A(i)(6)(F) of the Act (setting forth the exception for remuneration that promotes access to care and poses a low risk of harm to patients and Federal health care programs).

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one drug to treat a disease.²³ However, the Subsidy Program proposed by Requestor differs materially from the lawful avenues described in our prior guidance.

In the course of reviewing this request, we found certain publicly available information that relates to the subject of this request for an advisory opinion that was not provided by Requestor but informs our conclusion about the fraud and abuse risks posed by the Proposed Arrangement.²⁴ Therefore, we first provide additional context—otherwise available to the public—in this analysis.

1. Additional Publicly Available Background Information

According to a study published in 2020, Requestor’s Medications constitute the most expensive cardiovascular drug ever launched in the United States.²⁵ The study concluded that treating all eligible patients with the Disease with the Medications (n=120,000) would increase health care spending in the United States by \$32.3 billion a year, with nearly all of the budget impact resulting from the cost of the Medications.²⁶ With respect to the annual increase in spending of \$32.3 billion, the study explained that:

[t]his includes a \$31.9 billion increase in annual prescription drug expenditures, which would increase the total US spending for all prescription drugs by 9.3% (from \$344 billion in 2018 to \$375.9 billion).[]
As diagnosis rates increase, as a result of greater awareness about ATTR-

²³ OIG, Special Advisory Bulletin on Patient Assistance Programs for Medicare Part D Enrollees, 70 Fed. Reg. 70,623, 70,626 (Nov. 22, 2005), [available at https://oig.hhs.gov/fraud/docs/alertsandbulletins/2005/2005PAPSpecialAdvisoryBulletin.pdf](https://oig.hhs.gov/fraud/docs/alertsandbulletins/2005/2005PAPSpecialAdvisoryBulletin.pdf) (hereinafter the “2005 Bulletin”); [see also OIG, Supplemental Special Advisory Bulletin: Independent Charity Patient Assistance Programs, 79 Fed. Reg. 31,120 \(May 30, 2014\), available at https://oig.hhs.gov/fraud/docs/alertsandbulletins/2014/independent-charity-bulletin.pdf](https://oig.hhs.gov/fraud/docs/alertsandbulletins/2014/independent-charity-bulletin.pdf) (hereinafter the “2014 Bulletin”).

²⁴ We conducted an appropriate independent inquiry to better inform our understanding of the Medications and the Disease as it relates to our assessment of the Proposed Arrangement. [See 42 C.F.R. § 1008.39\(d\).](#)

²⁵ Dhruv S. Kazi et al., [Cost-Effectiveness of Tafamidis Therapy for Transthyretin Amyloid Cardiomyopathy](https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.119.045093), Circulation. 2020;141:1,214–24 (originally published Apr. 14, 2020), [available at https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.119.045093](https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.119.045093).

²⁶ [Id.](#) at 1,220.

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CM, increased use of nuclear scintigraphy for accurate diagnosis, and more widespread uptake of genetic tests to screen family members of individuals with variant ATTR-CM, the budget impact of tafamidis is expected to increase as well.²⁷

A recent commentary in *JAMA Cardiology* co-authored by an investigator on the Medications' pivotal phase 3 clinical trial also raised concerns regarding pricing of the Medications.²⁸ Further, according to these authors, current estimates that the prevalence of the Disease is approximately 100,000 people in the United States "may be a substantial underestimate of the number of patients eligible for" the Medications.²⁹

We likewise take into consideration our recent enforcement history involving conduct by pharmaceutical manufacturers—vis-à-vis foundations that operate assistance programs—that the United States alleged was illegal. To date, the United States has settled enforcement actions totaling more than \$900 million against ten pharmaceutical manufacturers, including Requestor,³⁰ and four foundations, for conduct solely involving the allegedly illegal use of foundations that operate patient assistance programs as conduits for improper payments to patients.³¹ Central to these allegations is a concern

²⁷ [Id.](#) (internal citations omitted).

²⁸ Gurwitz JH, Maurer MS. [Tafamidis—A Pricey Therapy for a Not-So-Rare Condition](#). *JAMA Cardiol.* 2020;5(3):247–248, 248 doi:10.1001/jamacardio.2019.5233, available at <https://jamanetwork.com/journals/jamacardiology/article-abstract/2758314?resultClick=1> ("[T]he very high prices for [the Medications] are not justified and appear to be a particularly egregious example of price gouging.").

²⁹ [Id.](#) at 247.

³⁰ See DOJ, Press Release, [Pfizer Agrees to Pay \\$23.85 Million to Resolve Allegations that it Paid Kickbacks Through a Co-Pay Assistance Foundation](#) (May 24, 2018), available at <https://www.justice.gov/usao-ma/pr/pfizer-agrees-pay-2385-million-resolve-allegations-it-paid-kickbacks-through-co-pay>; OIG, [Corporate Integrity Agreement between the Office of Inspector General of the Department of Health and Human Services and Pfizer Inc.](#) (May 23, 2018), available at https://oig.hhs.gov/fraud/cia/agreements/Pfizer_Inc_05232018.pdf.

³¹ See, e.g., DOJ, Press Release, [Novartis Agrees to Pay Over \\$51 Million to Resolve Allegations that It Paid Kickbacks Through Co-Pay Foundations](#) (July 1, 2020), available at <https://www.justice.gov/usao-ma/pr/novartis-agrees-pay-over-51-million-resolve-allegations-it-paid-kickbacks-through-co-pay> (noting that the United States has collected over \$900 million from ten pharmaceutical companies relating to similar conduct); DOJ,

that pharmaceutical manufacturers blunt the impact of patient cost sharing to induce patients to fill prescriptions for costly medications. This, in turn, removes a potential downward pressure on the price of the drugs. Most of these settlements involved concurrent execution of integrity agreements with the OIG.³²

2. Federal Anti-Kickback Statute

In evaluating the Proposed Arrangement under the Federal anti-kickback statute, we look to whether it would involve remuneration to an individual to induce that individual to purchase an item or service for which payment may be made under a Federal health care program. The Proposed Arrangement plainly would. Specifically, under the Subsidy Program, Requestor would provide remuneration in the form of a valuable Subsidy Card to eligible Medicare beneficiaries. To be eligible, a Medicare beneficiary must, among other criteria, be prescribed one of the Medications for treatment of the Disease, meet certain financial need criteria, and be enrolled in a Part D or MA-PD plan that provides coverage for the Medications. These beneficiaries would, in turn, use the Subsidy Card at the point of sale to pay virtually all of the cost-sharing obligations that would otherwise apply for the Medications. In this respect, the Subsidy Program would operate as a quid pro quo—Requestor would offer remuneration (the Subsidy Card) to the beneficiary in return for the beneficiary purchasing one of the Medications.³³ We note also that the Subsidy Card can only be used to pay for Medicare cost-sharing obligations specific to the Medications; it has no value outside of these cost-sharing obligations, and it cannot be used to assist with expenses related to the other medical needs of beneficiaries diagnosed with the Disease (e.g., prescription drugs used by the patient in

Press Release, [Fourth Foundation Resolves Allegations that it Conspired with Pharmaceutical Companies to Pay Kickbacks to Medicare Patients](#) (Jan. 21, 2020), available at <https://www.justice.gov/usao-ma/pr/fourth-foundation-resolves-allegations-it-conspired-pharmaceutical-companies-pay> (explaining that four foundations have paid a total of \$13 million to settle similar allegations).

³² None of these settlement agreements with the Department of Justice or associated integrity agreements with the OIG involve any admission of wrongdoing by any pharmaceutical manufacturer or foundation.

³³ Any definitive conclusion regarding a prohibited quid pro quo would require consideration of a party’s intent when implementing the Proposed Arrangement, which has not yet occurred.

connection with managing the Disease, treating symptoms of the Disease, or treating pain and other side effects of the Disease).³⁴

Requestor certified that beneficiary cost-sharing obligations for the Medications are approximately \$13,000 per year, and Requestor identified inability to pay these cost-sharing obligations as an impediment to a significant portion of Medicare beneficiaries purchasing the Medications. Requestor designed the Subsidy Program to address this impediment. Thus, the Subsidy Card would be offered to beneficiaries to induce them to purchase a covered item by removing what would otherwise be an impediment that would deter such purchase.³⁵ Based on Requestor’s certifications, a beneficiary would know about the availability of the Subsidy Program at the time he or she purchases the Medications. Accordingly, where a Medicare beneficiary otherwise may be unwilling or unable to purchase the Medications due to his or her cost-sharing obligations, which are driven by the list price of the Medications, the Subsidy Program would induce that beneficiary to purchase the Medications by removing the financial impediment, and the Medicare program would bear the costs for the Medications.³⁶ Using the language of the Federal anti-kickback statute, Requestor proposes to provide remuneration (the Subsidy

³⁴ We also note that Requestor has identified foundations that operate patient assistance programs that presently have funds covering amyloidosis. The Disease is a type of amyloidosis.

³⁵ As we have stated previously, “[t]he meaning of the term ‘to induce,’ which describes the intent of those who offer or pay remuneration in paragraph (2) of the [anti-kickback] statute, is found in the ordinary dictionary definition: ‘to lead or move by influence or persuasion,’” which reflects the “congressional intent to create a very broadly worded prohibition.” 56 Fed. Reg. 35,952 (July 29, 1991), available at <https://oig.hhs.gov/fraud/docs/safeharborregulations/072991.htm>.

³⁶ Among the arguments advanced by Requestor in its request for this advisory opinion is that “offering co-pay assistance to help eligible patients afford a clinically-appropriate medication, when such medication is the only approved medication for the disease and the principal reason that patients would not fill their prescriptions is their inability to pay their out-of-pocket costs, does not improperly induce the underlying prescribing decisions.” We disagree with Requestor’s formulation of the legal standard. The central inquiry here is whether one purpose of the remuneration offered and provided by Requestor is to induce the beneficiary to purchase the Medications. If, as Requestor’s formulation indicates, the principal reason a beneficiary would not fill a prescription is inability to pay the out-of-pocket expenses, then remuneration that would address that inability to pay would, without question, influence the patient’s purchasing decision.

Card) to a person (the Medicare beneficiary) to induce that person to purchase an item (the Medications) reimbursable under a Federal health care program (Medicare).³⁷

There is no statutory exception or regulatory safe harbor to the Federal anti-kickback statute that would apply to protect the remuneration offered under the Proposed Arrangement.³⁸ Absent any protection under a statutory exception or regulatory safe harbor, we examine whether the Proposed Arrangement would pose more than a minimal risk of fraud and abuse under the anti-kickback statute. While the Proposed Arrangement could help individual beneficiaries access the Medications, this potential benefit neither: (i) changes the fact that the Proposed Arrangement plainly would involve remuneration to an individual to induce that individual to purchase an item for which payment may be made under a Federal health care program; nor (ii) sufficiently mitigates the risks of fraud and abuse present in the Proposed Arrangement. In particular, where, as here, a manufacturer offers remuneration (the Subsidy Card) contingent on the purchase of its products, the remuneration presents many of the traditional risks of fraud and abuse that the anti-kickback statute is designed to prevent, including increased costs to Federal health care programs (e.g., through elimination of beneficiary sensitivity towards the price of the Medications); beneficiary steering and anti-competitive effects; and interference with or skewing of clinical decision making.

In light of these risks, and for the combination of the following reasons, we conclude that the Proposed Arrangement would present more than a minimal risk of fraud and abuse under the Federal anti-kickback statute; indeed, we find the Proposed Arrangement highly suspect under the Federal anti-kickback statute because one purpose of the Subsidy Program—perhaps the primary purpose—would be to induce Medicare beneficiaries to purchase Requestor’s federally reimbursable Medications.

³⁷ Any definitive conclusion regarding a violation of the anti-kickback statute would require consideration of a party’s intent when implementing the Proposed Arrangement, which has not yet occurred.

³⁸ There is a statutory exception to the Federal anti-kickback statute that protects certain non-routine waivers by pharmacies of cost-sharing obligations. Section 1128B(b)(3)(G) of the Act (42 U.S.C. § 1320a-7b(b)(3)(G)); see also 42 C.F.R. § 1001.952(k)(3) (implementing the statutory exception for a pharmacy’s waiver of beneficiary copayment, coinsurance, and deductible amounts). This statutory exception and regulatory safe harbor do not apply to the Subsidy Program because Requestor is not a pharmacy. Moreover, insofar as Requestor would reimburse the pharmacy on behalf of the Medicare beneficiary, the Proposed Arrangement would operate as a subsidy, rather than a waiver, of the beneficiary’s cost-sharing obligations.

a. Risk of Improper Increased Costs to the Medicare Program

The Proposed Arrangement could improperly increase overall costs to the Medicare program by insulating Medicare beneficiaries from the economic effects of the cost of the Medications, thereby abrogating a market safeguard that Congress included to protect against inflated drug prices.

i. Requestor's List Price

In evaluating the risk of increased costs, we cannot ignore that the initial list price for the Medications—which Requestor set—has been characterized as the most expensive cardiovascular drug ever launched in history, and the facts and circumstances here suggest that the implementation of the Proposed Arrangement, in conjunction with other assistance available to patients, is critical to Requestor's ability to maintain the price at this level.³⁹ The fact that a new treatment will generate costs to the Federal health care programs in absolute terms is not relevant to our analysis. All treatments generate costs to the Federal health care programs. However, where the projected costs are derived from pricing terms that necessitate the subsidization of cost-sharing obligations for beneficiaries, information about the projected costs is directly relevant to our analysis.

While we do not express any opinion as to the appropriateness of the Medications' list price, we cannot ignore how the Proposed Arrangement would operate to drive up costs to the Medicare program by providing remuneration to beneficiaries to shield them from the economic impacts of the list price and, in so doing, influence their decision to purchase the Medications.⁴⁰ We cautioned against this specific concern in our 2005 Bulletin, where we observed:

[C]ost-sharing subsidies can be very profitable for manufacturers, providing additional incentives for abuse. So long as the manufacturer's sales price for the product exceeds its marginal variable costs plus the amount of the cost-sharing assistance, the manufacturer makes a profit.

³⁹ As noted above, Requestor's Medications alone could “increase the total US spending for all prescription drugs by 9.3%” if all patients with the Disease were prescribed—and purchased—the Medications. Dhruv S. Kazi et al., Cost-Effectiveness of Tafamidis Therapy for Transthyretin Amyloid Cardiomyopathy, *Circulation*. 2020;141:1214–24, (originally published Feb. 12, 2020), available at <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.119.045093>.

⁴⁰ Id.

These profits can be considerable, especially for expensive drugs for chronic conditions.⁴¹

Moreover, we believe there is a significant risk that the Proposed Arrangement could be used to support future increases in the list price, further driving up costs to Federal health care programs and resulting in additional harm to the Medicare fisc.

ii. Abrogation of Part D Program Safeguard

There is a significant risk that the Proposed Arrangement would effectively abrogate statutory cost-sharing requirements under the Medicare Part D program. Specifically, the design of the Proposed Arrangement appears to be calibrated to circumvent one of the key pricing controls (exposing beneficiaries to the economic effects of drug pricing)⁴²

⁴¹ 2005 Bulletin, 70 Fed. Reg. at 70,626.

⁴² See Congress of the United States, Congressional Budget Office, A Detailed Description of CBO's Cost Estimate for the Medicare Prescription Drug Benefit (July 2004), available at <https://www.cbo.gov/sites/default/files/108th-congress-2003-2004/reports/07-21-medicare.pdf>. Specifically, with respect to its estimate for the Medicare prescription drug benefit, the Congressional Budget Office stated:

CBO assumed that even the most aggressive use of cost-management tools by drug plans would be unlikely to keep prices for some drugs from rising as a result of a Medicare drug benefit. By reducing the cost to consumers of obtaining covered drugs, the new Medicare drug benefit would correspondingly make Medicare enrollees . . . less sensitive to drug prices. For instance, if a drug's target population consisted mainly of Medicare beneficiaries and close substitutes for that drug did not exist, the manufacturer could raise the drug's price—or, in the case of a new drug, could enter the market with a higher launch price. The loss in sales resulting from that price hike would not be large enough to reduce the manufacturer's profit, however, because beneficiaries would pay only a portion of that higher price. Preventing such price hikes would be difficult without imposing direct price controls or threatening to deny or delay coverage of the drug. Most drugs, however, face competition from close substitutes, and the most likely effect of a Medicare drug benefit would be modest price increases for the subset of drugs that had patent protection or exclusive marketing rights. CBO modeled that ‘price effect’ as a function of drug spending by enrollees who previously did not have prescription drug coverage . . . CBO estimated that the cost-sharing requirements of the [Medicare Prescription Drug, Improvement, and Modernization Act of 2003] would limit the extent of that price effect. Beneficiaries . . . would still face the full negotiated price of the drugs they purchased before they reached their

that Congress instituted in its design of the standard Medicare Part D prescription drug benefit and would lay bare the dangers of removing this market safeguard.⁴³

Simply put, the Proposed Arrangement would leave Requestor's price for the Medications unbridled by a key market constraint inherent to the Medicare Part D drug benefit design, while the Medicare program and taxpayers bear the financial brunt of an unchecked drug price. It is not appropriate for pharmaceutical manufacturers to use remuneration that would be prohibited by the Federal anti-kickback statute as a backdoor way to sidestep the cost-sharing requirements that Congress included in the standard Part D benefit.

iii. Elimination of Cost-Sharing Obligations for Almost All Medicare Beneficiaries

We view the Subsidy Program holistically with other assistance that would be available to Medicare beneficiaries who are prescribed the Medications to demonstrate the potentially improper impact on costs to the Federal health care programs. Requestor certified that the majority of patients who may be prescribed the Medications will be Medicare beneficiaries. Requestor further certified that the cost-sharing obligations present a prohibitive financial barrier for a significant proportion of these Medicare patients. The Subsidy Program would eliminate any meaningful cost-sharing obligations and, operating in conjunction with Requestor's free drug program and the Medicare Low-Income Subsidy, would mean all but approximately 9 percent of Medicare beneficiaries who are prescribed one of the Medications would be able to purchase it without incurring any significant out-of-pocket costs.⁴⁴ Nonetheless, under the Proposed Arrangement,

deductible and when their spending fell between their initial coverage limit and the catastrophic threshold. Even after they reached the catastrophic threshold, beneficiaries would generally face some coinsurance and thus would not be completely insulated from price increases.

Id.

⁴³ See generally section 1860D-2(b) of the Act; see also 2005 Bulletin, 70 Fed. Reg. at 70,626 ("Inflated prices could have a 'spillover' effect on the size of direct subsidies, reinsurance payments, and risk corridor payments paid by Medicare to Part D plans in future years, potentially resulting in higher costs to the Medicare program.") (internal citations omitted).

⁴⁴ As discussed in section I(B)(1), supra, approximately 91 percent of Medicare beneficiaries have a household income below 800 percent of the FPL, which is the upper income threshold of the Subsidy Program. Those beneficiaries falling between 500

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Requestor would continue to be paid for, and the Medicare program would continue to bear the cost of, the Medications purchased by all beneficiaries who do not qualify for Requestor's free drug program (including beneficiaries who qualify for the Subsidy Program and beneficiaries who qualify for the Medicare Low-Income Subsidy).

We also note that, in our guidance related to patient assistance programs operated by foundations, we explained that funds that have generous financial need criteria, particularly when a fund is limited to a subset of available drugs or the drugs of a major donor, could be evidence of intent to fund a substantial part of the cost sharing for a particular drug for the purpose of inducing the use of that drug.⁴⁵ The same concern holds true for purposes of the Subsidy Program, which establishes financial need thresholds that, operating in conjunction with Requestor's free drug program and the Medicare Low-Income Subsidy, ensure that approximately 91 percent of Medicare beneficiaries would not have any significant out-of-pocket costs associated with the Medications.

Requestor also certified that, based on 2019 thresholds, many Medicare beneficiaries would reach the catastrophic phase with their first purchase of the Medications and that the Subsidy Program is designed to move these beneficiaries into the catastrophic phase of the Part D benefit. Our concern regarding increased costs to the Medicare program is magnified where, as here, the Proposed Arrangement would hasten Medicare beneficiaries' progression to the catastrophic phase, where the Medicare program pays 80 percent of the costs for pharmacological therapies through reinsurance, in addition to the money the Medicare program has already paid plans to deliver the Part D drug benefit.⁴⁶

b. Risk of Patient Steering and Anti-Competitive Effects

We have longstanding concerns that cost-sharing subsidies provided by a pharmaceutical manufacturer can: (i) have the practical effect of steering beneficiaries to, and locking

percent and 800 percent of the FPL would be eligible for the Subsidy Program. Those with household incomes below 500 percent of the FPL, which is the lower income threshold of the Subsidy Program, would be eligible for either the Medicare Low-Income Subsidy or Requestor's free drug program. This leaves only approximately nine percent of Medicare beneficiaries (*i.e.*, those with incomes above 800 percent of the FPL) responsible for paying the full cost-sharing amounts when purchasing these Medications.

⁴⁵ 2014 Bulletin, 79 Fed. Reg. at 31,122.

⁴⁶ See 2005 Bulletin, 70 Fed. Reg. at 70,625–26.

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them into, the manufacturer's product; and (ii) lead to anti-competitive effects.⁴⁷ We believe it would be ill-advised to draw a conclusion with respect to the Proposed Arrangement without considering the facts certified by Requestor surrounding existing treatments for, and potential future advances in treating, the Disease. In addition, the patient's decision to purchase the Medications does not occur in a vacuum; a critical prerequisite to such decision is the treating physician's decision to order (or not to order) a prescription for the Medications. In this respect, Requestor acknowledged that “[t]here is no question that some physicians may consider drug costs and a patient's out-of-pocket burden when making prescribing judgments.” We agree, and we anticipate that the treating physician will consider the costs and the availability of the Subsidy Program when determining the preferred treatment option for a patient. Likewise, because Requestor has set the list price at \$225,000 for each annual course of treatment, we fully expect patients to consider the cost of the Medications—as well as the availability of the Subsidy Program—in evaluating the Medications over an alternative option. In light of these circumstances, we conclude that Requestor's Subsidy Program would present more than a minimal risk of steering beneficiaries to, and locking them into, the Medications.

The fact that the Medications are the only FDA-approved pharmacological therapy for the Disease as of today does not alleviate our concerns regarding patient steering and anti-competitive effects. By Requestor's own certifications, patients and their health care providers presently have a choice when selecting a treatment for the Disease and may have additional treatment options in the future. More specifically, Requestor described two medications that physicians have prescribed off-label to treat patients with the Disease and indicated that they are aware of physicians opting to prescribe one of these medications because it is covered under Medicare Part B, for which a beneficiary may have Medigap coverage to defray cost-sharing obligations.⁴⁸ We understand that

⁴⁷ Id. at 70,626.

⁴⁸ Requestor certified that the list price for these alternative pharmacological treatments is higher than the list price for the Medications. We note, however, that our concerns regarding patient steering derive from the relative costs of treatment options to the beneficiary, rather than the relative costs to the Medicare program. In addition, even if the alternative treatments are more expensive to the Medicare program, that fact does not alleviate our concern that the Subsidy Program would inappropriately increase overall costs to the Medicare program by insulating Medicare beneficiaries from the economic effects of the price of the Medications. In other words, the increased costs to the Medicare program would be a direct result of the improper remuneration in the Subsidy Program. Finally, we note that, standing alone, the fact that the list price of an alternative pharmacological treatment may be higher than the list price of the Medications is not determinative of overall costs to Federal health care programs for the various pharmacological treatment alternatives; any comparison of total costs would likely

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physicians may also consider non-pharmacological treatments (e.g., organ transplants) as an option for at least some patients with the Disease, but we recognize the complexity and severity of these treatments means they may not be a feasible option for many beneficiaries. We take no position on the effectiveness of one treatment over another; we only highlight that where a patient may have a choice in treatment, and the Subsidy Program is designed to influence that choice, there is more than a minimal risk that the remuneration (the Subsidy Card) would steer patients to the Medications.

In addition, the fact that there is no other FDA-approved pharmacological therapy for the Disease available today does not foreclose the possibility that new treatments will emerge, nor that new treatments could be less expensive or equally (or more) effective. Indeed, Requestor's certifications indicate that FDA approval of a competitor therapy in 2021 is a possibility. Even so, Requestor asserted its view that, even if the FDA were to approve another therapy for the treatment of the Disease, "if the Medications demonstrate superior efficacy and safety" then that superior efficacy and safety would be relevant to the fraud and abuse analysis of the Proposed Arrangement in the same way the lack of FDA-approved alternatives is now. We disagree. The Subsidy Program would virtually eliminate cost-sharing obligations for the Medications, which could inappropriately divert many beneficiaries with the Disease from any other treatment option—now or in the future—to the Medications because of the minimal out-of-pocket expenses when compared to those for other treatment options. In fact, we believe the Subsidy Program shares many of the risky features of problematic seeding programs insofar as it would steer patients to the Medications now so that these beneficiaries would continue to purchase the Medications in the future, even if other FDA-approved therapies emerge. Further, we believe that the Subsidy Program could negatively affect competition for as long as it remains in existence because it would give a financial advantage to the Medications over competing treatments, regardless of whether such other treatments are equally as effective.⁴⁹

require a complex economic analysis, the results of which would not address our concerns about the patient-steering risks of the Subsidy Program.

⁴⁹ "Ensuring fair competition in the health care marketplace is one of the goals of the anti-kickback statute." OIG, Medicare and State Health Care Programs: Fraud and Abuse; Clarification of the Initial OIG Safe Harbor Provisions and Establishment of Additional Safe Harbor Provisions Under the Anti-Kickback Statute, 64 Fed. Reg. 63,518, 63533 (Nov. 19, 1999), [available at https://oig.hhs.gov/fraud/docs/safeharborregulations/getdoc1.pdf](https://oig.hhs.gov/fraud/docs/safeharborregulations/getdoc1.pdf).

c. Potential Effects on Clinical Decision-Making

While remuneration that would induce a beneficiary to purchase the Medications, standing alone, would implicate the Federal anti-kickback statute, we also believe the remuneration offered under the Subsidy Program could affect a physician’s clinical decision-making, which is relevant to our assessment of the overall risk of the Proposed Arrangement. We recognize that the Proposed Arrangement would not involve remuneration to prescribers; rather, Requestor would offer remuneration to a Medicare beneficiary to induce the beneficiary to purchase the Medications. As discussed above, a critical prerequisite to such decision is the treating physician’s decision to order (or not to order) a prescription for the Medications, and Requestor acknowledged that “[t]here is no question that some physicians may consider drug costs and a patient’s out-of-pocket burden when making prescribing judgments.” In addition, as described above, Requestor certified that some physicians presently prescribe another pharmacological therapy instead of the Medications because the other treatment is a Part B drug, and some beneficiaries have purchased Medigap insurance policies that cover some or all of their Part B cost-sharing obligations.⁵⁰ Much like our conclusion that patients would consider the costs of the Medications in deciding their preferred treatment option with their physician, we likewise anticipate that some—if not most—physicians would consider a patient’s out-of-pocket costs for the Medications when deciding whether to prescribe them.

Requestor further certified that a physician must work with a beneficiary to enroll him or her in the Hub and may contact the Hub to find out about the Subsidy Program. The Hub also would communicate patient enrollment in the Subsidy Program to the patient’s prescribing physician (upon the prescriber’s request). Based on these facts, it is reasonable to anticipate that physicians would learn of the Subsidy Program soon after its implementation (e.g., through their first communication with the Hub) and, once a physician is aware of the program, every subsequent prescribing decision would be made with the knowledge that the Subsidy Program is available to minimize out-of-pocket costs for Medicare beneficiaries.

With this knowledge, we believe the Subsidy Program could affect the prescriber’s decision as to whether to order the Medications. To be clear, we are not suggesting that it is inappropriate for a physician to consider costs to patients; however, in these circumstances where Requestor has certified that cost-sharing obligations are the impediment to a significant portion of Medicare beneficiaries purchasing the

⁵⁰ Unlike Medigap insurance policies, which beneficiaries may choose to purchase to cover a variety of health care costs and which are a long-standing feature in the Medicare program that must follow requirements and standards set forth by Congress, the Subsidy Program is designed by Requestor in a way that would support the list price for its Medications while undermining the Part D benefit constructed by Congress.

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Medications, we believe that the availability of the Subsidy Card may impact the treating physician's clinical decision-making, *i.e.*, whether to prescribe the Medications for those beneficiaries. Moreover, both presently and if any new treatments emerge in the future—which Requestor certified could be as early as 2021—we believe there is a risk that the availability of the Subsidy Program could sway a physician to prescribe the Medications over any other treatment, even if such treatments are equally (or more) effective or have a lower overall cost.

3. Beneficiary Inducements CMP

In evaluating the Proposed Arrangement under the Beneficiary Inducements CMP, we consider whether Requestor would know or have reason to know that the remuneration it would offer to beneficiaries is likely to influence their selection of a particular provider, practitioner, or supplier for the order or receipt of any item or service for which payment may be made, in whole or in part, by Medicare or a State health care program. Here, we conclude that, although the Subsidy Card is clearly remuneration to a beneficiary, the Proposed Arrangement would not implicate the Beneficiary Inducements CMP.

a. Scope of Beneficiary Inducements CMP

As a threshold matter, we note that the Beneficiary Inducements CMP (section 1128A(a)(5) of the Act) contains a different, narrower prohibition than the Federal anti-kickback statute (section 1128B(b) of the Act) and uses a definition of “remuneration” that does not apply for purposes of the Federal anti-kickback statute. The Federal anti-kickback statute prohibits the knowing and willful offer, payment, solicitation, or receipt of any remuneration to induce or reward, among other things, referrals for, or purchases of, any item or service payable by a Federal health care program. In contrast, the Beneficiary Inducements CMP is focused on remuneration that the offeror knows or should know is likely to influence a beneficiary’s selection of a particular provider, practitioner, or supplier for items or services reimbursable by Medicare or a State health care program.

For purposes of the Beneficiary Inducements CMP, pharmaceutical manufacturers are not “providers, practitioners, or suppliers” unless they also own or operate, directly or indirectly, pharmacies, pharmacy benefits management companies, or other entities that file claims for payment under the Medicare or Medicaid programs.⁵¹ Here, Requestor is a pharmaceutical manufacturer, and it does not own or operate, directly or indirectly, any pharmacies that dispense the Medications. Therefore, Requestor is not a “provider,

⁵¹ OIG, Special Advisory Bulletin, Offering Gifts and Other Inducements to Beneficiaries (Aug. 2002), available at <https://oig.hhs.gov/fraud/docs/alertsandbulletins/SABGiftsandInducements.pdf>.

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practitioner, or supplier” for purposes of the Beneficiary Inducements CMP. Because Requestor is not a “provider, practitioner, or supplier,” the fact that the Subsidy Card would influence a beneficiary to purchase Requestor’s product (the Medications) would not implicate the Beneficiary Inducements CMP with respect to Requestor, notwithstanding the fact that this same remuneration stream would implicate the Federal anti-kickback statute.

b. Analysis of Proposed Arrangement

Where a pharmaceutical manufacturer offers remuneration to a beneficiary that the manufacturer knows or should know is likely to influence the beneficiary to select a particular provider, practitioner, or supplier (e.g., a physician or a pharmacy), that remuneration would implicate the Beneficiary Inducements CMP. In other words, a pharmaceutical manufacturer, such as Requestor, can be the offeror or transferor of remuneration that implicates (and violates) the Beneficiary Inducements CMP.⁵² However, based on the unique combination of facts presented in the Proposed Arrangement, we conclude that the remuneration offered by the Requestor under the Proposed Arrangement is not likely to influence a beneficiary to order the Medications from a particular provider, practitioner, or supplier.

First, under the Proposed Arrangement, Requestor would not make eligibility for the Subsidy Card dependent on the beneficiary’s use of certain prescribing providers or practitioners. Requestor certified that a beneficiary would be eligible to obtain a Subsidy Card regardless of which provider or practitioner prescribes the Medications, and Requestor has not provided any facts to indicate that a beneficiary’s ability to obtain a Subsidy Card would otherwise be impacted in any way by his or her selection of a particular provider or practitioner. Thus, based on the facts available to us, the remuneration that would be provided to beneficiaries under the Proposed Arrangement would not influence their selection of a particular prescribing provider or practitioner.

Second, Requestor would not make eligibility for the Subsidy Card dependent on the beneficiary’s use of a particular pharmacy. Specifically, the remuneration would not be conditioned on the beneficiary using a particular Dispensing Pharmacy, and the Subsidy Program would not give preference to any particular Dispensing Pharmacy. An eligible

⁵² See 2014 Bulletin, 79 Fed. Reg. at 31,121 (noting that a subsidy for cost-sharing obligations provided by a pharmaceutical manufacturer through an independent foundation’s patient assistance program may implicate the Beneficiary Inducements CMP, if the subsidy is likely to influence a Medicare or State health care program beneficiary’s selection of a particular provider, practitioner, or supplier, such as by making eligibility for the subsidy dependent on, for example, the patient’s use of certain prescribing physicians).

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beneficiary would be able to use the Subsidy Card at any Dispensing Pharmacy, and the amount of assistance that would be offered to a beneficiary under the Subsidy Program would not vary based on which Dispensing Pharmacy furnishes the Medications. That is, the Subsidy Program is structured such that the beneficiary would have the same limited cost-sharing obligation (\$35 per monthly fill) regardless of the Dispensing Pharmacy he or she selects to fill the prescription for the Medications. Thus, the remuneration would not influence the beneficiary's selection of one Dispensing Pharmacy over another Dispensing Pharmacy.⁵³

Requestor also certified that beneficiaries would have the opportunity to express a preference with respect to which Dispensing Pharmacy they use to obtain the Medications. Absent a preference, the Hub would select a Dispensing Pharmacy to fill a particular beneficiary's prescription based on the Dispensing Pharmacy with the lowest patient out-of-pocket costs or using a "round robin" process. While we recognize that some beneficiaries may face a more limited set of Dispensing Pharmacies to select from due to their Part D or MA-PD plans having a narrower list of Plan Pharmacies, that limitation is due to plan benefit design, not the remuneration offered by Requestor under the Proposed Arrangement. Any remuneration streams associated with such plan benefit designs are outside the scope of this advisory opinion.

Requester further certified that, to its knowledge, there has not been any instance where there were no Dispensing Pharmacies included among the preferred pharmacies in a beneficiary's Part D or MA-PD plan. Requester certified that, if such a circumstance were to arise, the Hub would send the prescription to the beneficiary's or the prescribing physician's preferred Dispensing Pharmacy. Absent a preference, the Hub would select a Dispensing Pharmacy to fill a particular beneficiary's prescription based on the Dispensing Pharmacy with the lowest patient out-of-pocket costs (that would otherwise be charged to the beneficiary but would instead, under the terms of the Subsidy Program, be paid for using the Subsidy Card) or using a "round robin" process.

In addition, Dispensing Pharmacies are the only pharmacies authorized by Requestor to dispense the Medications to any patient who wishes to purchase the Medications, regardless of whether the patient is eligible for the Subsidy Program. Thus, while we

⁵³ We contrast this with an arrangement where the nature or structure of the arrangement is such that the offeror knows or should know that the beneficiary would select a particular provider, practitioner, or supplier following the offer or transfer of the remuneration, e.g., an arrangement that requires a beneficiary to use the provider, practitioner, or supplier that is geographically closest to the beneficiary's location. If the Requestor structured the Subsidy Program in such a manner, then the Beneficiary Inducements CMP would be implicated, and no exception would apply.

recognize that the Subsidy Card may only be used at a Dispensing Pharmacy, it is not the Subsidy Program that dictates that limitation.⁵⁴

III. CONCLUSION

Based on the facts certified in your request for an advisory opinion and supplemental submissions, we conclude that: (i) the Proposed Arrangement, as structured, would not generate prohibited remuneration under the civil monetary penalty provision prohibiting inducements to beneficiaries, section 1128A(a)(5) of the Act; and (ii) the Proposed Arrangement would generate prohibited remuneration under the anti-kickback statute if the requisite intent to induce or reward referrals for, or purchases of, items and services reimbursable by a Federal health care program were present and that the OIG could potentially impose administrative sanctions on Pfizer Inc. under sections 1128(b)(7) or 1128A(a)(7) of the Act (as those sections relate to the commission of acts described in section 1128B(b) of the Act) in connection with the Proposed Arrangement. Any definitive conclusion regarding the existence of an anti-kickback violation requires consideration of all of the facts and circumstances of the arrangement as implemented, including a party's intent. Where, as is the case here, the arrangement is proposed but has not yet been implemented, we cannot reach a definitive conclusion regarding the existence of an anti-kickback violation.

IV. LIMITATIONS

The limitations applicable to this opinion include the following:

- This advisory opinion is issued only to Pfizer Inc., the requestor of this opinion. This advisory opinion has no application to, and cannot be relied upon by, any other individual or entity.
- This advisory opinion may not be introduced into evidence by a person or entity other than Pfizer Inc. to prove that the person or entity did not violate the provisions of sections 1128, 1128A, or 1128B of the Act or any other law.
- This advisory opinion is applicable only to the statutory provisions specifically noted above. No opinion is expressed or implied herein with

⁵⁴ We distinguish the facts here, where the Medications are available only through a limited number of Dispensing Pharmacies, from circumstances where remuneration influences beneficiaries to select a provider, practitioner, or supplier from a network over non-network providers, practitioners, or suppliers or where the value of remuneration to a beneficiary varies based on which provider, practitioner, or supplier the beneficiary selects. In such circumstances, the Beneficiary Inducements CMP would be implicated.

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respect to the application of any other Federal, state, or local statute, rule, regulation, ordinance, or other law that may be applicable to the Proposed Arrangement, including, without limitation, the physician self-referral law, section 1877 of the Act (or that provision's application to the Medicaid program at section 1903(s) of the Act).

- This advisory opinion will not bind or obligate any agency other than the U.S. Department of Health and Human Services.
- This advisory opinion is limited in scope to the specific arrangement described in this letter and has no applicability to other arrangements, even those which appear similar in nature or scope.
- No opinion is expressed herein regarding the liability of any party under the False Claims Act or other legal authorities for any improper billing, claims submission, cost reporting, or related conduct.

This opinion is also subject to any additional limitations set forth at 42 C.F.R. Part 1008. The OIG reserves the right to reconsider the questions and issues raised in this advisory opinion and, where the public interest requires, to rescind, modify, or terminate this opinion.

Sincerely,

ROBERT
DECONTI

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Robert K. DeConti
Assistant Inspector General for Legal Affairs



Transthyretin amyloidosis

Transthyretin amyloidosis is a slowly progressive condition characterized by the buildup of abnormal deposits of a protein called amyloid (amyloidosis) in the body's organs and tissues. These protein deposits most frequently occur in the peripheral nervous system, which is made up of nerves connecting the brain and spinal cord to muscles and sensory cells that detect sensations such as touch, pain, heat, and sound. Protein deposits in these nerves result in a loss of sensation in the extremities (peripheral neuropathy). The autonomic nervous system, which controls involuntary body functions such as blood pressure, heart rate, and digestion, may also be affected by amyloidosis. In some cases, the brain and spinal cord (central nervous system) are affected. Other areas of amyloidosis include the heart, kidneys, eyes, and gastrointestinal tract. The age at which symptoms begin to develop varies widely among individuals with this condition, and is typically between ages 20 and 70.

There are three major forms of transthyretin amyloidosis, which are distinguished by their symptoms and the body systems they affect.

The neuropathic form of transthyretin amyloidosis primarily affects the peripheral and autonomic nervous systems, resulting in peripheral neuropathy and difficulty controlling bodily functions. Impairments in bodily functions can include sexual impotence, diarrhea, constipation, problems with urination, and a sharp drop in blood pressure upon standing (orthostatic hypotension). Some people experience heart and kidney problems as well. Various eye problems may occur, such as cloudiness of the clear gel that fills the eyeball (vitreous opacity), dry eyes, increased pressure in the eyes (glaucoma), or pupils with an irregular or "scalloped" appearance. Some people with this form of transthyretin amyloidosis develop carpal tunnel syndrome, which is characterized by numbness, tingling, and weakness in the hands and fingers.

The leptomeningeal form of transthyretin amyloidosis primarily affects the central nervous system. In people with this form, amyloidosis occurs in the leptomeninges, which are two thin layers of tissue that cover the brain and spinal cord. A buildup of protein in this tissue can cause stroke and bleeding in the brain, an accumulation of fluid in the brain (hydrocephalus), difficulty coordinating movements (ataxia), muscle stiffness and weakness (spastic paralysis), seizures, and loss of intellectual function (dementia). Eye problems similar to those in the neuropathic form may also occur. When people with leptomeningeal transthyretin amyloidosis have associated eye problems, they are said to have the oculoleptomeningeal form.

The cardiac form of transthyretin amyloidosis affects the heart. People with cardiac amyloidosis may have an abnormal heartbeat (arrhythmia), an enlarged heart (cardiomegaly), or orthostatic hypertension. These abnormalities can lead to

progressive heart failure and death. Occasionally, people with the cardiac form of transthyretin amyloidosis have mild peripheral neuropathy.

Frequency

The exact incidence of transthyretin amyloidosis is unknown. In northern Portugal, the incidence of this condition is thought to be one in 538 people. Transthyretin amyloidosis is less common among Americans of European descent, where it is estimated to affect one in 100,000 people. The cardiac form of transthyretin amyloidosis is more common among people with African ancestry. It is estimated that this form affects between 3 percent and 3.9 percent of African Americans and approximately 5 percent of people in some areas of West Africa.

Causes

Mutations in the *TTR* gene cause transthyretin amyloidosis. The *TTR* gene provides instructions for producing a protein called transthyretin. Transthyretin transports vitamin A (retinol) and a hormone called thyroxine throughout the body. To transport retinol and thyroxine, four transthyretin proteins must be attached (bound) to each other to form a four-protein unit (tetramer). Transthyretin is produced primarily in the liver. A small amount of this protein is produced in an area of the brain called the choroid plexus and in the light-sensitive tissue that lines the back of the eye (the retina).

TTR gene mutations are thought to alter the structure of transthyretin, impairing its ability to bind to other transthyretin proteins and altering its normal function.

Inheritance Pattern

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

In most cases, an affected person inherits the mutation from one affected parent. Rarely, cases result from new mutations in the gene and occur in people with no history of the disorder in their family. Not all people who have a *TTR* gene mutation will develop transthyretin amyloidosis.

Other Names for This Condition

- Portuguese polyneuritic amyloidosis
- Portuguese type familial amyloid neuropathy
- Swiss type amyloid polyneuropathy
- type I familial amyloid polyneuropathy
- type II familial amyloid polyneuropathy

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
[/primer/testing/genetictesting](https://www.ncbi.nlm.nih.gov/primer/testing/genetictesting)
- Genetic Testing Registry: Amyloidogenic transthyretin amyloidosis
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C2751492/>

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22transthyretin+amyloidosis%22>

Other Diagnosis and Management Resources

- Boston University: Amyloid Treatment & Research Program
<http://www.bu.edu/amylويد/>
- GeneReview: Hereditary Transthyretin Amyloidosis
<https://www.ncbi.nlm.nih.gov/books/NBK1194>
- MedlinePlus Encyclopedia: Autonomic neuropathy
<https://medlineplus.gov/ency/article/000776.htm>

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Autonomic neuropathy
<https://medlineplus.gov/ency/article/000776.htm>
- Health Topic: Amyloidosis
<https://medlineplus.gov/amyloidosis.html>
- Health Topic: Arrhythmia
<https://medlineplus.gov/arrhythmia.html>
- Health Topic: Autonomic Nervous System Disorders
<https://medlineplus.gov/autonomicnervoussystemdisorders.html>
- Health Topic: Eye Diseases
<https://medlineplus.gov/eyediseases.html>
- Health Topic: Peripheral Nerve Disorders
<https://medlineplus.gov/peripheralnervedisorders.html>

Genetic and Rare Diseases Information Center

- Familial transthyretin amyloidosis
<https://rarediseases.info.nih.gov/diseases/656/familial-transthyretin-amylodosis>
- Hereditary amyloidosis
<https://rarediseases.info.nih.gov/diseases/6611/hereditary-amylodosis>

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Orthostatic Hypotension Information Page
<https://www.ninds.nih.gov/Disorders/All-Disorders/Orthostatic-hypotension-Information-Page>

Educational Resources

- MalaCards: amyloidosis, hereditary, transthyretin-related
https://www.malacards.org/card/amyloidosis_hereditary_transthyretin_related
- Merck Manual Home Edition for Patients and Caregivers: Amyloidosis
<https://www.merckmanuals.com/home/hormonal-and-metabolic-disorders/amyloidosis/amyloidosis>
- Neuromuscular Disease Center, Washington University
<https://neuromuscular.wustl.edu/nother/amyloid.htm#transthyretin>
- Orphanet: Familial amyloid polyneuropathy
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=85447

Patient Support and Advocacy Resources

- Amyloidosis Foundation
<https://amyloidosis.org/>
- Amyloidosis Support Groups
<https://www.amyloidosissupport.org/>
- Family Caregiver Alliance
<https://www.caregiver.org/>
- Metabolic Support UK
<https://www.metabolicsupportuk.org/>
- National Organization for Rare Disorders (NORD): Amyloidosis
<https://rarediseases.org/rare-diseases/amyloidosis/>
- The Foundation for Peripheral Neuropathy
<https://www.foundationforpn.org/>

Clinical Information from GeneReviews

- Hereditary Transthyretin Amyloidosis
<https://www.ncbi.nlm.nih.gov/books/NBK1194>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28transthyretin+amyloidosis%5BTIAB%5D%29+OR+%28familial+amyloid+polyneuropathy%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1440+days%22%5Bdp%5D>

Catalog of Genes and Diseases from OMIM

- AMYLOIDOSIS, HEREDITARY, TRANSTHYRETIN-RELATED
<http://omim.org/entry/105210>

Medical Genetics Database from MedGen

- Amyloidogenic transthyretin amyloidosis
<https://www.ncbi.nlm.nih.gov/medgen/414031>

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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/14987380>

Reprinted from Genetics Home Reference:

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U.S. National Library of Medicine

National Institutes of Health

Department of Health & Human Services

STATE-OF-THE-ART REVIEW



Screening for Transthyretin Amyloid Cardiomyopathy in Everyday Practice

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HIGHLIGHTS

- ATTR-CM is a life-threatening, progressive disease that is often underdiagnosed and misdiagnosed.
- Certain clinical scenarios have been identified that now warrant screening for ATTR-CM.
- Once ATTR-CM is suspected, a definitive diagnosis can usually be achieved noninvasively.
- Accurate, early diagnosis of ATTR-CM is key to enabling appropriate patient care.

ABSTRACT

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a life-threatening, progressive, infiltrative disease caused by the deposition of transthyretin amyloid fibrils in the heart, and can often be overlooked as a common cause of heart failure. Delayed diagnosis due to lack of disease awareness and misdiagnosis results in a poorer prognosis. Early accurate diagnosis is therefore key to improving patient outcomes, particularly in the context of both the recent approval of tafamidis in some countries (including the United States) for the treatment of ATTR-CM, and of other promising therapies under development. With the availability of scintigraphy as an inexpensive, noninvasive diagnostic tool, the rationale to screen for ATTR-CM in high-risk populations of patients is increasingly warranted. Here the authors propose a framework of clinical scenarios in which screening for ATTR-CM is recommended, as well as diagnostic "red flags" that can assist in its diagnosis among the wider population of patients with heart failure. (J Am Coll Cardiol HF 2019;7:709-16)

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ABBREVIATIONS AND ACRONYMS

AL = light-chain amyloidosis

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRm = hereditary transthyretin amyloidosis

ATTRwt = wild-type transthyretin amyloidosis

CMR = cardiac magnetic resonance

EKG = electrocardiogram

HFpEF = heart failure with preserved ejection fraction

Tc = technetium

TTR = transthyretin protein

TTR = transthyretin gene

Transthyretin amyloid cardiomyopathy (ATTR-CM) represents 1 of the 2 most common types of cardiac amyloidosis, an infiltrative heart muscle disease caused by extracellular deposition of misfolded proteins which form insoluble amyloid fibrils (1,2). ATTR-CM is a life-threatening, progressive disease that can affect the heart in isolation or as part of a systemic disorder (2-4). The other main type of cardiac amyloidosis is light-chain (AL) amyloidosis, which arises from overproduction and misfolding of monoclonal immunoglobulin light chains (2). AL amyloidosis is a relatively rare disease, characterized by a rapidly progressive clinical course which, if untreated, has a median survival of <6 months (5).

ATTR-CM is caused by deposition of transthyretin (TTR), a plasma protein predominantly produced in the liver, which is responsible for transporting thyroxine and retinol (1,6). TTR mainly exists in a tetrameric state, but destabilizing mutations in the transthyretin gene (*TTR*) and/or aging promote its proteolytic remodeling and dissociation into monomers which subsequently misfold and aggregate to form amyloid fibrils that deposit in tissues (1,2,4,6). In the case of ATTR-CM, amyloid fibrils mainly deposit in the interstitial space of the myocardium leading to increased wall thickness and diastolic dysfunction that can result in heart failure (HF) and arrhythmias (2).

ATTR-CM exists as 1 of 2 subtypes, defined by the precursor TTR protein. Hereditary, or mutant, ATTR (ATTRm) amyloidosis is caused by the presence of *TTR* mutations, resulting in a less stable TTR protein (1). Wild-type ATTR (ATTRwt) amyloidosis, previously referred to as “senile systemic amyloidosis,” is a result of age-related changes in wild-type TTR stability (1,4,7).

EPIDEMIOLOGY OF ATTRm. The prevalence of ATTRm is difficult to establish due to the variable geographical distribution of *TTR* mutations. Some mutations are endemic in certain regions, but recent estimates suggest that the prevalence in Europe is <1 in 100,000 (8). Conversely, although endemic in

some areas of Japan, the overall prevalence in Japan is thought to be much lower, approximately 1 in 1,000,000 (9). The valine 122 isoleucine substitution *TTR* mutation most commonly affects individuals of Sub-Saharan African ancestry and has an allele prevalence of 3% to 4% within the African-American population (10).

EPIDEMIOLOGY OF ATTRwt. Recent data suggest that ATTR-CM is overlooked as a cause of common cardiovascular conditions in older people, with relatively high rates among individuals diagnosed with HF with preserved ejection fraction (HFpEF) (11), low-flow aortic stenosis, and settings of increased wall thickness (3). Additionally, autopsy data have shown that among adults 80 years of age or older, 25% have significant TTR amyloid deposits in the myocardium (12). Despite being historically considered a disease of older age, there have been reports of diagnosis of ATTRwt in patients as young as 47 years (13). Although the exact prevalence of ATTRwt is unknown, it is almost certainly the most common cause of cardiac amyloidosis, particularly in the elderly, potentially accounting for up to 10% of elderly patients with HF (1,4). With a convenient and relatively inexpensive imaging modality, bone scintigraphy, having strong evidence as an accurate, noninvasive approach to diagnosing ATTR-CM (14,15), the number of patients identified as having this condition will undoubtedly increase in the future.

ATTR-CM MANIFESTATIONS AND MANAGEMENT

Although ATTR-CM commonly presents with symptoms of HF or arrhythmias, amyloidosis is a systemic disease and can cause various noncardiac symptoms (3,16). Ophthalmological, neurological, and gastrointestinal symptoms can all be extracardiac signs of cardiac amyloidosis, particularly in ATTRm (1,16). Medical management of ATTR-CM remains a significant unmet need, with treatments for ATTR-CM currently being limited to the alleviation of HF symptoms, including sodium restriction or aldosterone antagonists in combination with loop diuretics (2,4). Heart transplantation alone or, in some ATTRm patients, in combination with liver transplantation, is

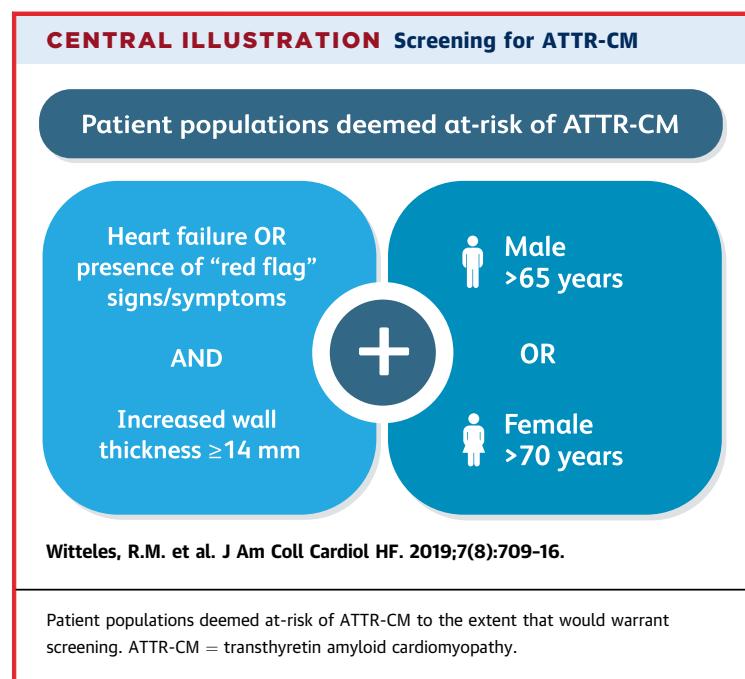
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an option for selected patients, but there are major limitations to these approaches, including transplantation eligibility, extracardiac organ involvement, limited organ supply, and post-transplantation complications (1,3,4,17). Until recently, there were no approved pharmacological therapies for use in patients with ATTR-CM. Based on positive phase III clinical trial results, tafamidis, a TTR stabilizer, has been approved in some countries for the treatment of hereditary and wild-type forms of ATTR-CM (18,19). Another TTR stabilizer has shown promising results in a recent phase II trial (20), and favorable results in clinical trials testing gene silencing compounds for neurologic dysfunction in ATTRm (21,22) suggest that other pharmacologic approaches may also be effective in managing ATTR-CM in the future.

DELAY TO DIAGNOSIS AND MISDIAGNOSIS OF ATTR-CM

Early diagnosis of ATTR-CM is key, as prognosis worsens rapidly with continued amyloid deposition and subsequent advancing organ dysfunction (3). However, diagnosis is often delayed owing to low disease awareness or misdiagnosis, which can be attributed to the previously perceived rarity of the disease, fragmented knowledge, erroneous beliefs around diagnosis and treatment, the heterogenic and multisystemic nature of the disease, and symptom overlap with other conditions (1,3,7). As a result, a high index of clinical suspicion is paramount to facilitate early and accurate diagnosis (7,23). Typically, a patient's cardiac disease progresses during the period of unidentified ATTR-CM, which is most often unrecognized during its early symptomatic stage. Diagnosis mostly occurs in the later stages of disease following the manifestation of serious cardiac symptoms (23,24).

The impact of ATTR-CM symptoms on a patient's quality of life can be significant, and the disease is associated with financial burden and professional difficulties (25). In a survey of ATTR-CM patients, 17% of all respondents reported visiting 5 different physicians before receiving the correct diagnosis. More than 50% of ATTRm and 39% of ATTRwt patients received a misdiagnosis; of those 76% and 75%, respectively, received treatment for the misdiagnosed condition (26). Additionally, a recent study from 2 European amyloidosis centers showed that 35% of ATTRwt patients had been previously misdiagnosed with other conditions, with hypertensive heart disease being the most frequent misdiagnosis (27). The result of misdiagnosis is, therefore, not only a prolonged time to appropriate patient management



strategies, but also the risk of inappropriate treatments (28). Typical antihypertensive and HF treatments such as beta blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor antagonists are ineffective in cardiac amyloidosis patients, and often lead to clinical worsening (1,29). Moreover, other drugs such as digoxin and calcium channel blockers are relatively contraindicated in cardiac amyloidosis patients (1).

It is therefore crucial that physicians are aware, not only of ATTR-CM, but also of appropriate assessments, diagnostic tools, and clues within the patient's medical and family history that can help to elucidate etiology; this is of particular importance in light of the approval of tafamidis by the United States Food and Drug Administration (FDA) and in other countries (19), and of several emerging therapies which offer future treatment options for a disease which previously had none (13).

A clear framework of possible clinical scenarios and subsequent assessments is needed to aid in the identification of those at risk of having undetected ATTR-CM.

CLINICAL SCENARIOS AND "RED FLAGS" FOR ATTR-CM

A proposed disease identification framework, established by an international panel of 11 amyloidosis experts, is presented here. A list of clinical scenarios and red flags were proposed and considered by a working group of experts in the field. Their

FIGURE 1 Further Evidence to Support a Suspicion of ATTR-CM

“Red flags” for ATTR-CM

-  Reduction in longitudinal strain with apical sparing
-  Discrepancy between left ventricular thickness and QRS voltage (with a lack of left ventricular hypertrophy on EKG)
-  Atrioventricular block, in the presence of increased left ventricular wall thickness
-  Echocardiographic hypertrophic phenotype with associated infiltrative features, including increased thickness of the atrioventricular valves, interatrial septum and right ventricular free wall
-  Marked extracellular volume expansion, abnormal nulling time for the myocardium or diffuse late gadolinium enhancement on CMR
-  Symptoms of polyneuropathy and / or dysautonomia
-  History of bilateral carpal tunnel syndrome
-  Mild increase in troponin levels on repeated occasions

“Red flags” that further support the possibility of an underlying ATTR-CM. ATTR-CM = transthyretin amyloid cardiomyopathy; CMR = cardiac magnetic resonance imaging; EKG = electrocardiogram.

subsequent discussions evaluated the language used to describe the clinical scenarios, their suitability for reflecting an underlying ATTR-CM, and usefulness to raise suspicion to define patient characteristics that would warrant screening for ATTR-CM (**Central Illustration**), and additional red flags that may help to further heighten suspicion or support the possibility of an underlying ATTR-CM as part of general clinical practice (**Figure 1**).

When developing a screening tool to aid in the recognition of a disease, one should consider the disease prevalence; the ease, impact, and accuracy of diagnostic testing; and the potential for effective treatment. In the case of ATTR-CM, prevalence is

likely higher than initially thought (15), bone scintigraphy represents a low-cost, low-impact diagnostic test (14), and there is now a drug approved by the FDA and in other countries with proven efficacy and safety in a phase III clinical trial (18,19), with others in development (1). Therefore, a broad screening approach to identify ATTR-CM is recommended within certain clinical scenarios (**Central Illustration**).

CLINICAL SCENARIOS THAT WOULD WARRANT SCREENING FOR ATTR-CM

The most common symptom of ATTR-CM is HF (1). Increased wall thickness caused by amyloid fibril deposition is a prominent characteristic of ATTR-CM (4) and can lead to ventricular stiffening and left ventricle diastolic dysfunction. One study showed that, in a cohort of 120 Caucasian patients aged ≥ 60 years with increased left ventricular wall thickness ≥ 12 mm admitted for HFrEF, 13.3% suffered from ATTRwt (11).

A significant male predominance has been reported in both ATTRwt (approximately 85% to 95%) and ATTRm, with a clear association between increased age and both ATTRwt and the most common types of ATTRm mutations (23,30,31). More recent findings have also suggested that a wider age range might be affected, as well as a higher proportion of female patients than previously recognized (13,27). As an example of the recently recognized increased involvement among women is that in the above-mentioned HFrEF cohort, 50% of identified ATTRwt patients were female (11).

Furthermore, in a cohort of predominantly male Caucasian patients (76%) with increased left ventricular wall thickness ≥ 15 mm, ATTRm was found in 7.6% of patients older than 55 years, including only 1.6% of patients aged 55 to 64 years, but 11.1% and 11.3% of patients aged 65 to 74 years and 75 to 84 years, respectively (32). Therefore, screening suspected individuals older than the age of 65 years with increased left ventricular wall thickness is particularly recommended.

Based on these values, the expert panel believe that the clinical scenarios of increased wall thickness with either HF or red flag signs/symptoms (see below) in men older than 65 years or women older than 70 years are expected to represent a significant rate of diagnosis, supporting the investigation of disease etiology through screening of these patients.

RED FLAGS FOR ATTR-CM

Clinical clues or red flags that should further heighten suspicion or alert clinicians to the possibility of

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ATTR-CM as an underlying condition are listed in **Figure 1**. The presence of any of these red flags together with increased left ventricular wall thickness should lead to screening as described in **Figure 2**.

ECHOCARDIOGRAPHY. Echocardiography revealing a reduction in longitudinal strain with relative apical sparing can help to distinguish cardiac amyloidosis from other causes of increased left ventricular wall thickness (33).

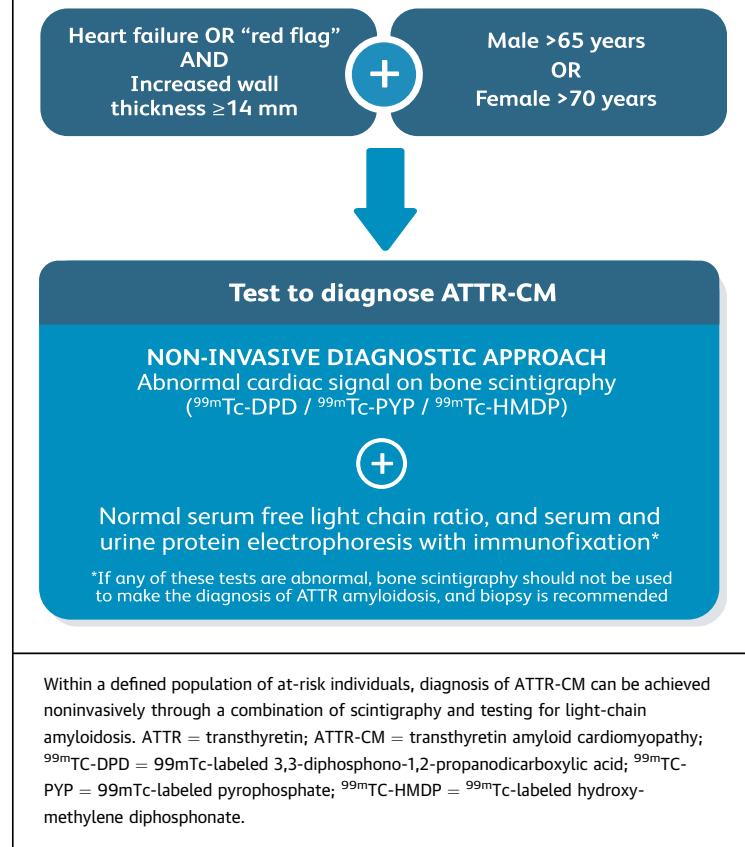
ELECTROCARDIOGRAPHY. Another clue to cardiac amyloidosis is the discrepancy between left ventricular wall thickness and QRS voltages on a standard 12-lead electrocardiogram (EKG); although low voltages on an EKG in the setting of increased left ventricular wall thickness is a classic feature of cardiac amyloidosis, many ATTR-CM patients do not have frankly low voltages, but instead have a discrepancy between the presence of left ventricular hypertrophy on imaging with normal, or low-normal, voltages on EKG (3,4).

Atrioventricular block is another indicative feature of ATTR-CM and may be seen in up to 22% of patients with cardiac amyloidosis (34). Cardiac conduction abnormalities may be the first manifestation of ATTR-CM, and amyloid infiltration of the sinus and atrioventricular nodes may necessitate pacemaker implantation (1). A recent referral for a pacemaker for atrioventricular block, in the presence of left ventricular hypertrophy, should therefore raise clinical suspicion of ATTR-CM.

CARDIAC MAGNETIC RESONANCE. Suspicion for hypertrophic cardiomyopathy with evidence of infiltrative features, such as pericardial effusion, atrioventricular block, interatrial septal and valvular thickening, and apical sparing of longitudinal strain are all suggestive of ATTR-CM (3). Myocardial deposition of amyloid fibrils increases the extracellular volume and results in the accumulation of exogenous gadolinium contrast, seen with cardiac magnetic resonance (CMR) (3,4). Marked extracellular volume expansion, abnormal nulling time for the myocardium, and diffuse late gadolinium enhancement on CMR are, especially in combination, highly suspicious of ATTR-CM.

SYSTEMIC SYMPTOMS. The coexistence of systemic symptoms involving the peripheral and/or autonomic nervous system along with cardiac dysfunction are important clues to the presence of ATTR-CM (17) – although this is less common in ATTRm patients with the valine 122 isoleucine mutation (7), which is prevalent in the United States (35). Bilateral sensory-motor polyneuropathy that begins in the lower limbs and follows an ascending pattern, dysautonomia in

FIGURE 2 Achieving a Noninvasive Diagnosis of ATTR-CM



the form of orthostatic hypotension, diarrhea/constipation and erectile dysfunction, and eye involvement such as glaucoma, intravitreal deposition, and scalloped pupils, may be present in ATTRm (1). Carpal tunnel syndrome, lumbar spinal stenosis, and bicep tendon rupture are all common extracardiac manifestations in wild-type ATTR-CM. Bilateral carpal tunnel syndrome is often 1 of the earliest indicators of ATTR-CM, is the most common noncardiac manifestation (1,17,24), and can precede clinical HF by several years (2). A recent study found it present in approximately 50% of individuals with ATTRwt 5 to 7 years before diagnosis (36). Lumbar spinal stenosis and traumatic bicep tendon rupture have also been identified as clinical manifestations of extracardiac amyloid deposition in ATTRwt (1,37,38).

BIMARKERS. Serum troponin levels are often persistently elevated (2), and, in the absence of an apparently severe cardiomyopathy on echocardiogram, should raise suspicion of ATTR-CM. N-terminal pro-B-type natriuretic peptide is also nearly always elevated in cases of cardiac amyloidosis (1,2), often disproportionately for the degree of HF.

TABLE 1 Serum and Urine Tests to Rule Out AL Amyloidosis*

Test	What Does it Detect?	Most Sensitive Test for:	Normal Range
SPIE†	Clonal immunoglobulin and/or clonal light chain	Confirming clonal immunoglobulin production	No M-spike present
UPIE†	Clonal immunoglobulin and/or clonal light chain	Confirming clonal light chain production	No M-spike present
Serum free light chain assay	Ratio of serum kappa:lambda light chains	Detecting low-level clonal light chain production; clonality assumed if ratio is far from 1:1	Kappa:lambda ratio = 0.26–1.65‡

*If any of these tests are abnormal, bone scintigraphy should not be used to make the diagnosis of ATTR amyloidosis, and biopsy is recommended. †SPIE and UPIE are more sensitive than protein electrophoresis without immunofixation and should be ordered as the preferred tests. ‡In patients with kidney disease, mild elevations in the kappa:lambda ratio are frequently encountered. In the setting of a normal SPIE/UPIE, a kappa:lambda ratio up to 2.5 can typically be considered normal.

AL = light-chain; ATTR = transthyretin amyloidosis; SPIE = serum protein electrophoresis with immunofixation; UPIE = urine protein electrophoresis with immunofixation.

ACHIEVING A DEFINITIVE DIAGNOSIS OF ATTR-CM

Once ATTR-CM is suspected, a timely, definitive diagnosis is recommended. On average, ATTR-CM patients have an approximate survival of 3 to 5 years from diagnosis (39), with the median survival time in ATTRm ranging from 26 to 62 months (35,40,41), and the median survival time in ATTRwt ranging from 43 to 67 months from diagnosis (13,30,31,35,40) and 73 months from symptom onset (31). Features ascertained from electrocardiography, echocardiography, CMR, and cardiac biomarkers are routinely used to identify cardiac abnormalities (3), and neurologic, ophthalmologic, and gastrointestinal assessments can help to identify noncardiac symptoms (7). A diagnosis can and should be achieved as soon as possible once suspicion has been raised, and noninvasive approaches to definitively diagnose ATTR-CM are available (Figure 2).

BONE SCINTIGRAPHY. Bone scintigraphy is a highly sensitive imaging technique that is used to evaluate the distribution of active bone formation in the body (42). Scintigraphy with technetium (Tc)-labelled bisphosphonates localizes to TTR cardiac amyloid deposits, although the molecular basis for this remains unknown (15). 99mTc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid, 99mTc-labeled pyrophosphate, and 99mTc-labeled hydroxymethylene diphosphonate have all shown high sensitivity and specificity for imaging cardiac TTR amyloid (15). The sensitivity of a positive scan alone for detecting TTR amyloid deposits was >99%, with a specificity of 86% in a large international study with more than 1,200 individuals. False-positive results were found mostly in AL amyloidosis patients (15).

RULING OUT AL AMYLOIDOSIS. Gillmore et al. (15) have shown that cardiac localization of radiotracer

in bone scintigraphy can occur in approximately 30% of patients with AL amyloidosis, which can confound the distinction between cardiac amyloidosis etiologies. As the survival of untreated patients with AL amyloidosis with cardiac involvement may be <6 months (5), and given the availability of disease modifying therapies for AL amyloidosis (2), ruling out this disease should be considered a clinical priority. This can be achieved through measuring the proportion of kappa:lambda light chains with the serum free light chain assay, and testing for immunofixation electrophoresis of serum and urine. The combination of serum and urine immunofixation and quantification of serum free light chains has a 99% sensitivity for identifying AL amyloidosis (3). Serum and urine protein electrophoresis should always be performed with immunofixation to increase the sensitivity of the assays for detecting low-level monoclonal proteins (Table 1). In the absence of a detectable monoclonal protein or an abnormal serum free light chain ratio, the specificity of bone scintigraphy for ATTR-CM is 100% (15).

BIOPSY. Traditionally, a definitive diagnosis of amyloidosis has been obtained through tissue biopsy stained with Congo red, which shows pathognomonic green birefringence of amyloid deposits when viewed under polarized light (3,15). Although the historic gold standard for diagnosis of cardiac amyloidosis was through endomyocardial biopsy (4,7), this invasive approach requires expertise and carries potential risks (43). Extracardiac biopsy specimens, such as abdominal fat pad, can yield a diagnosis in some patients, but the diagnostic accuracy can be particularly low in ATTR amyloidosis due to a high false-negative rate (3,44). Currently, histologic confirmation is still needed in cases where both bone scintigraphy and tests for monoclonal protein (suggestive of possible AL amyloidosis) are abnormal, to confirm and type amyloid deposits by immunohistochemistry or mass spectrometry. Given that between approximately 2% to 8% of the general population older than 65 years of age exhibit findings compatible with monoclonal gammopathy of undetermined significance (45), this is not a rare scenario in the evaluation of a patient with suspected ATTRwt amyloidosis. We recommend mass spectrometry as the preferred method for amyloid typing in most cases, as immunohistochemistry findings are often subtle and can be misinterpreted if not in very experienced hands (46).

GENETIC TESTING. Given that it is not possible to reliably distinguish between ATTRm and ATTRwt by clinical or histologic techniques, TTR gene

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sequencing is recommended for the definitive diagnosis in all forms of confirmed ATTR-CM (1).

CONCLUSIONS

ATTR-CM represents a significant burden to patients and health care systems alike, particularly as it is associated with protracted diagnosis, or misdiagnosis, leading to delays in the application of appropriate management strategies. Generally low levels of disease awareness coupled with heterogeneity of clinical manifestations have resulted in suboptimal recognition and identification of ATTR-CM. Traditional, invasive diagnostic tools are no longer deemed necessary to achieve definitive diagnosis for most patients, owing to the diagnostic accuracy of bone scintigraphy. Given the recent approval of tafamidis by the FDA and in other countries based on a positive ATTR-CM phase III trial, with further promising therapies in development, it is important to correctly identify patients. Within this current framework, a

series of clinical scenarios and clues that should raise suspicion of ATTR-CM, and diagnostic approaches, have been outlined.

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Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

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ABSTRACT

BACKGROUND

Transthyretin amyloid cardiomyopathy is caused by the deposition of transthyretin amyloid fibrils in the myocardium. The deposition occurs when wild-type or variant transthyretin becomes unstable and misfolds. Tafamidis binds to transthyretin, preventing tetramer dissociation and amyloidogenesis.

METHODS

In a multicenter, international, double-blind, placebo-controlled, phase 3 trial, we randomly assigned 441 patients with transthyretin amyloid cardiomyopathy in a 2:1:2 ratio to receive 80 mg of tafamidis, 20 mg of tafamidis, or placebo for 30 months. In the primary analysis, we hierarchically assessed all-cause mortality, followed by frequency of cardiovascular-related hospitalizations according to the Finkelstein–Schoenfeld method. Key secondary end points were the change from baseline to month 30 for the 6-minute walk test and the score on the Kansas City Cardiomyopathy Questionnaire—Overall Summary (KCCQ-OS), in which higher scores indicate better health status.

RESULTS

In the primary analysis, all-cause mortality and rates of cardiovascular-related hospitalizations were lower among the 264 patients who received tafamidis than among the 177 patients who received placebo ($P<0.001$). Tafamidis was associated with lower all-cause mortality than placebo (78 of 264 [29.5%] vs. 76 of 177 [42.9%]; hazard ratio, 0.70; 95% confidence interval [CI], 0.51 to 0.96) and a lower rate of cardiovascular-related hospitalizations, with a relative risk ratio of 0.68 (0.48 per year vs. 0.70 per year; 95% CI, 0.56 to 0.81). At month 30, tafamidis was also associated with a lower rate of decline in distance for the 6-minute walk test ($P<0.001$) and a lower rate of decline in KCCQ-OS score ($P<0.001$). The incidence and types of adverse events were similar in the two groups.

CONCLUSIONS

In patients with transthyretin amyloid cardiomyopathy, tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations and reduced the decline in functional capacity and quality of life as compared with placebo. (Funded by Pfizer; ATTR-ACT ClinicalTrials.gov number, NCT01994889.)

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*The complete list of the ATTR-ACT Study Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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TRANSTHYRETIN AMYLOID CARDIOMYOPATHY is a life-threatening disease characterized by the accumulation of amyloid fibrils composed of misfolded transthyretin protein in the heart.¹ Misfolded monomers or oligomers of transthyretin are deposited in the myocardium, leading to cardiomyopathy and symptoms of heart failure, including dyspnea, fatigue, orthostatic hypotension, and syncope.² Infiltration of the conduction system can lead to bundle-branch block, atrioventricular block, sinoatrial disease, and atrial fibrillation.

Transthyretin amyloid cardiomyopathy is a late-onset disease; symptoms are predominately manifested in male patients 60 years of age or older.² The condition can be inherited as an autosomal dominant trait caused by pathogenic mutations in the transthyretin gene *TTR* (ATTRm) or by the deposition of wild-type transthyretin protein (ATTRwt), previously called senile systemic amyloidosis.³ There are more than 120 pathogenic mutations in *TTR* that result in a variable phenotypic presentation.^{2,3} Although the prevalence of ATTRwt is uncertain, studies that use an approach to diagnosis that is not based on biopsy^{4,5} have reported a prevalence of 13% among patients with heart failure with a preserved ejection fraction,⁶ 16% among patients undergoing transcatheter aortic-valve replacement for severe aortic stenosis,⁷ and 5% among patients with presumed hypertrophic cardiomyopathy.⁸ Treatments have been limited to supportive care, with no guideline-recommended treatment. Median survival in untreated patients is reported to be 2.5 years after diagnosis for ATTRm caused by the *TTR* Val122Ile mutation and 3.6 years for ATTRwt.^{9,10} Death in most patients is from cardiac causes, including sudden death and heart failure.⁹

Transthyretin is a 127-amino acid, 55-kD protein that is primarily synthesized in the liver and transports thyroxine and retinol-binding protein-retinol (vitamin A) complex.^{11,12} Fibrillogenesis occurs when the tetrameric structure of the transthyretin protein dissociates into intermediates, which misassemble into soluble oligomers, protofilaments, and amyloid fibrils.¹³ Kelly and colleagues discovered that a polymorphism in *TTR* that encodes the amino-acid substitution Thr119Met stabilized the protein in the context of a destabilizing pathogenic variant (Val30Met), leading to the development of tafamidis,^{14,15} a benzoxazole derivative lacking nonsteroidal anti-

inflammatory drug activity that binds to the thyroxine-binding sites of transthyretin with high affinity and selectivity and inhibits the dissociation of tetramers into monomers. Tafamidis has been shown to slow the progression of peripheral neurologic impairment in transthyretin amyloid polyneuropathy.¹⁶

With respect to transthyretin amyloid cardiomyopathy, a phase 2, open-label trial involving 31 patients showed that tafamidis (20 mg daily) stabilized transthyretin and had an acceptable safety profile.¹⁷ A single-center, nonrandomized study showed an association between tafamidis and improved survival.¹⁸ The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT)¹⁹ was designed to determine the efficacy and safety of tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy.

METHODS

TRIAL OVERSIGHT

ATTR-ACT was a phase 3, multicenter, international, parallel-design, placebo-controlled, double-blind, randomized trial. Details of the trial have been described previously.¹⁹ The trial was overseen by a steering committee that included investigators and the sponsor. ATTR-ACT was approved by the independent review board or ethics committee at each participating site and was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent. The trial was designed by the sponsor in collaboration with clinicians with experience in the treatment of transthyretin amyloid cardiomyopathy. Investigators collected and held the data in a blinded fashion until the data were analyzed centrally by the sponsor. An external data and safety monitoring board was responsible for monitoring patient safety and conducted unblinded reviews of cumulative trial data. An independent, end-point adjudication committee, whose members were also unaware of the trial-group assignments, determined whether investigator-reported events met the definition of disease-related efficacy end points with the use of predefined end-point criteria, thereby maintaining the scientific integrity of the trial. The statistical analysis was performed by the sponsor, and data tables were provided to the investiga-

tors. All authors participated in the interpretation of the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. The first author wrote the first draft. All authors participated in manuscript development and made the decision to publish the results. Agreements between the sponsor of the trial, Pfizer, and the investigators included data confidentiality.

PATIENTS

Patients between 18 and 90 years of age were eligible to participate in ATTR-ACT if they had transthyretin amyloid cardiomyopathy (ATTRwt or ATTRm) confirmed by the presence of amyloid deposits on analysis of biopsy specimens obtained from cardiac and noncardiac sites (e.g., fat aspirate, gastrointestinal sites, salivary glands, or bone marrow) and, in patients without ATTRm, by the presence of transthyretin precursor protein confirmed on immunohistochemical analysis, scintigraphy, or mass spectrometry. Cardiac involvement was confirmed by means of echocardiography, with an end-diastolic interventricular septal wall thickness exceeding 12 mm; a history of heart failure, with at least one prior hospitalization for heart failure or clinical evidence of heart failure (without hospitalization) manifested in signs or symptoms of volume overload or elevated intracardiac pressures requiring treatment with a diuretic for improvement; an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level greater than or equal to 600 pg per milliliter; and a 6-minute walk-test distance exceeding 100 m.

Patients were excluded if any one of the following criteria was met: they had, in the opinion of the investigator, heart failure that was not due to transthyretin amyloid cardiomyopathy; New York Heart Association (NYHA) class IV heart failure; the presence of light-chain amyloidosis; a history of liver or heart transplantation; an implanted cardiac device; previous treatment with tafamidis; an estimated glomerular filtration rate lower than 25 ml per minute per 1.73 m² of body-surface area; or liver transaminase levels exceeding two times the upper limit of the normal range. Patients were also excluded if they had severe malnutrition as defined by a modified body-mass index (mBMI) of less than 600, calculated as the serum albumin level in grams per liter multiplied by the conventional BMI (the weight in kilograms

divided by the square of the height in meters), or were receiving concurrent treatment with nonsteroidal antiinflammatory drugs, tauroursodeoxycholate, doxycycline, calcium-channel blockers, or digitalis.

TRIAL DESIGN

Patients were randomly assigned to receive 80 mg of tafamidis, 20 mg of tafamidis, or matching placebo once daily in ratio of a 2:1:2. Stratification was conducted according to TTR status (variant or wild type) and baseline NYHA class. An interactive Web-response system was used. The trial duration was 30 months, and on completion patients were offered enrollment in an extension study. Patients who had adverse events that may have been associated with treatment and may have affected adherence to the dosing regimen or continued participation in the trial were given the option to receive a reduced dose (patients receiving a dose of 80 mg would instead receive a dose of 40 mg, and all others continued to receive the dose assigned at randomization).

ANALYSIS POPULATIONS

The modified intention-to-treat analysis included all patients who were enrolled, received at least one dose of tafamidis or placebo, with both patient and investigator unaware of group assignment, and underwent at least one postbaseline efficacy evaluation (i.e., postbaseline hospitalization, study visit, or death). The safety analysis set included all enrolled patients who received at least one dose of tafamidis or placebo. Because all patients who were enrolled also fulfilled the three other criteria of the modified intention-to-treat analysis, this analysis was effectively also an intention-to-treat analysis.

OUTCOMES

We hierarchically assessed all-cause mortality, followed by frequency of cardiovascular-related hospitalizations over the course of the 30-month trial. This analysis compared the results of a pooled tafamidis (80 mg and 20 mg) treatment group with the placebo group. Key secondary end points were change from baseline to month 30 in both distance walked on the 6-minute walk test,²⁰ a measure of functional capacity, and the Kansas City Cardiomyopathy Questionnaire—Overall Summary (KCCQ-OS) score,²¹ which assesses quality of life. Scores range from 0 to 100, with lower

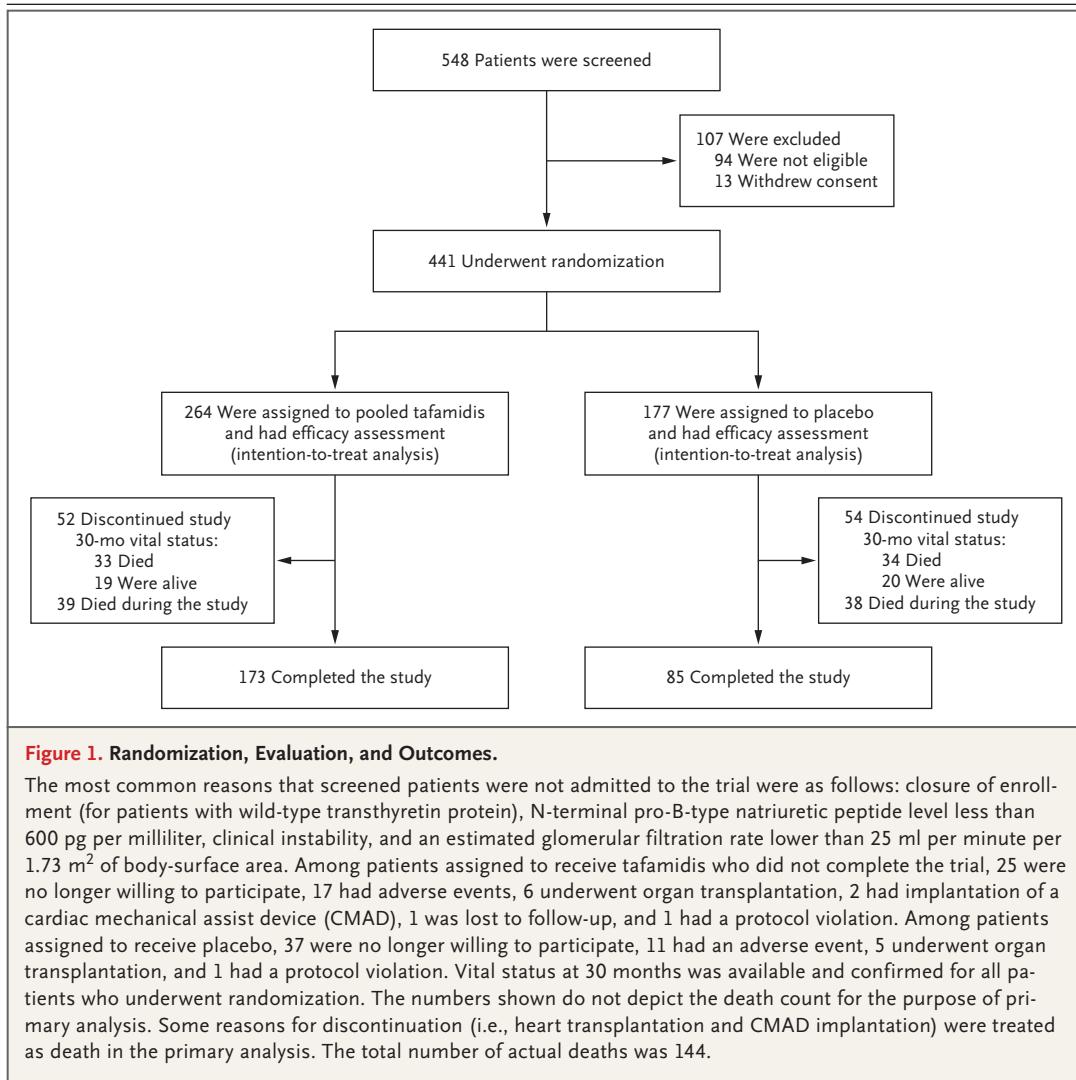


Figure 1. Randomization, Evaluation, and Outcomes.

The most common reasons that screened patients were not admitted to the trial were as follows: closure of enrollment (for patients with wild-type transthyretin protein), N-terminal pro-B-type natriuretic peptide level less than 600 pg per milliliter, clinical instability, and an estimated glomerular filtration rate lower than 25 ml per minute per 1.73 m² of body-surface area. Among patients assigned to receive tafamidis who did not complete the trial, 25 were no longer willing to participate, 17 had adverse events, 6 underwent organ transplantation, 2 had implantation of a cardiac mechanical assist device (CMAD), 1 was lost to follow-up, and 1 had a protocol violation. Among patients assigned to receive placebo, 37 were no longer willing to participate, 11 had an adverse event, 5 underwent organ transplantation, and 1 had a protocol violation. Vital status at 30 months was available and confirmed for all patients who underwent randomization. The numbers shown do not depict the death count for the purpose of primary analysis. Some reasons for discontinuation (i.e., heart transplantation and CMAD implantation) were treated as death in the primary analysis. The total number of actual deaths was 144.

scores denoting poorer quality of life. Vital status at month 30 was assessed for all enrolled patients.

STATISTICAL ANALYSIS

A sample size of 400 patients was estimated to give the trial power of at least 90% to detect a 30% reduction in mortality, a reduction in the frequency of cardiovascular-related hospitalizations from 2.5 to 1.5 (over the 30-month duration of the trial), or both given treatment with tafamidis. Our trial population was targeted to comprise at least 30% of patients with ATTRm and at least 30% with ATTRwt. Comparisons were based on the pooled tafamidis treatment groups of 80 mg and 20 mg versus placebo, except for specific dose comparisons. In the primary analysis,

we hierarchically assessed all-cause mortality, followed by frequency of cardiovascular-related hospitalizations with the use of the Finkelstein-Schoenfeld method,²² which is based on the principle that each patient in the clinical trial is compared with every other patient within each stratum in a pairwise manner. This method gives a higher importance to all-cause mortality. The pairwise comparison proceeds in hierarchical fashion, using all-cause mortality, followed by frequency of cardiovascular-related hospitalization when patients cannot be differentiated on the basis of mortality. In the analysis of frequency of cardiovascular-related hospitalization, when two patients had different follow-up times, the shorter follow-up time was used in compar-

ing the frequency of their cardiovascular-related hospitalizations.

We applied the Finkelstein–Schoenfeld method to the patients stratified according to NYHA class at baseline (class I or II vs. class III) and TTR status (variant vs. wild-type), yielding four stratification pools. Heart transplantation, heart and liver transplantation, and implantation of a mechanical cardiac-assist device were treated as death for the purposes of this analysis. Only one patient underwent liver transplantation alone, and this event was not treated as a death. All-cause mortality was analyzed with the use of a Cox proportional-hazards model, with treatment and the stratification factors treated as covariates.

We compared the frequency of cardiovascular-related hospitalizations with the use of a Poisson regression model, with treatment, TTR status (variant and wild type), NYHA baseline class (NYHA classes I and II combined vs. NYHA class III), treatment-by-TTR status interaction, and treatment-by-NYHA baseline class interaction terms as factors, with adjustment for treatment duration. The key secondary end points were assessed with the use of a mixed-effect model, repeated-measure approach and analysis of covariance,²³ with an unstructured covariance matrix. Center and patient-within-center were treated as random effects, and treatment, visit, TTR status (ATTRm vs. ATTRwt), and visit-by-treatment interaction were treated as fixed effects, with the baseline value as covariate. A prespecified hierarchical testing order (the 6-minute walk test, followed by the KCCQ-OS) provided multiplicity protection against type 1 error. The remaining secondary and exploratory analyses and end points were not adjusted for multiplicity.

RESULTS

PATIENT CHARACTERISTICS

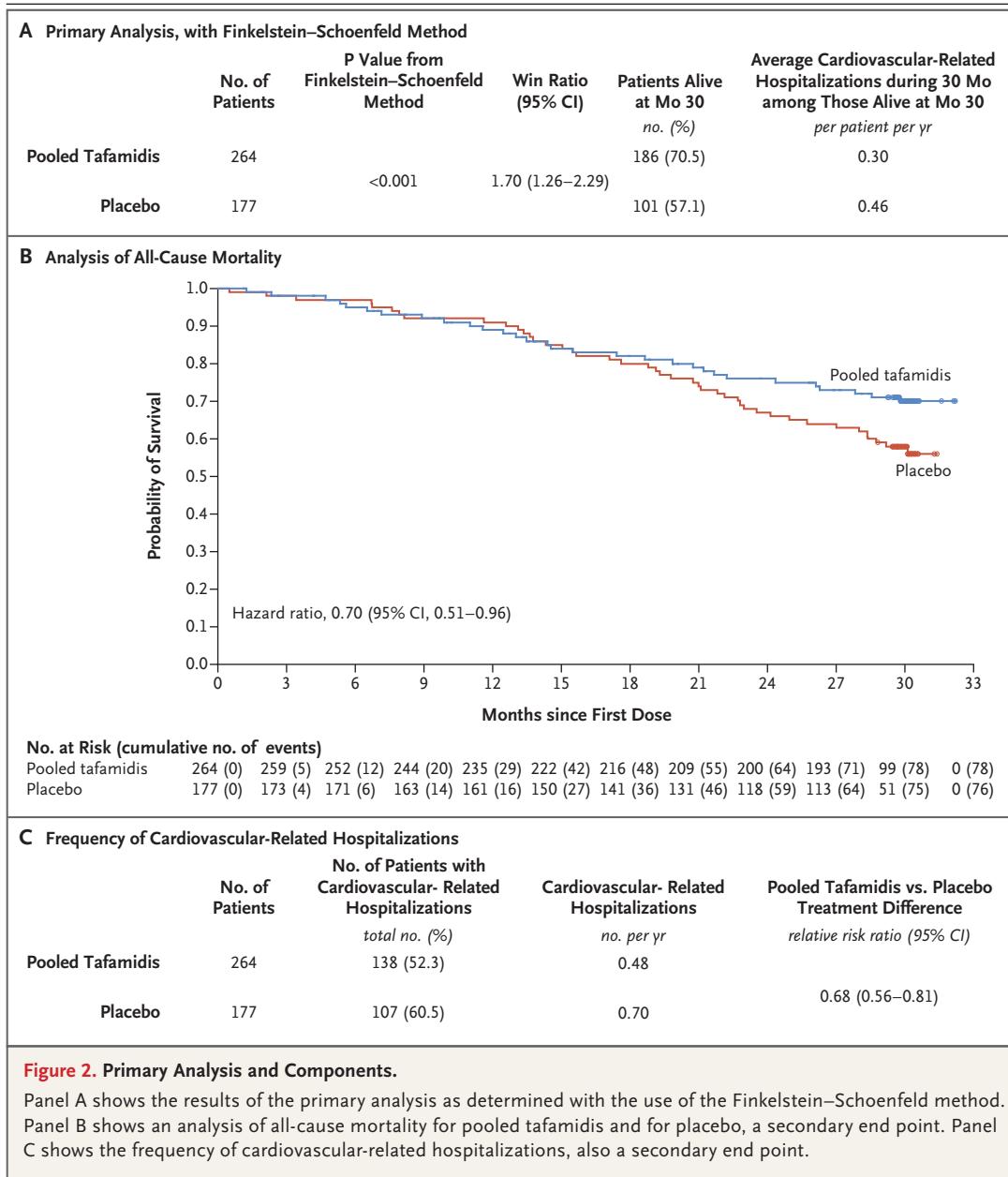
From December 2013 through August 2015, a total of 548 patients were screened and 441 patients enrolled at 48 sites in 13 countries; 264 patients received tafamidis (80 mg or 20 mg) and 177 patients received placebo (Fig. 1; and Table S1 in the Supplementary Appendix, available at NEJM.org). Overall, baseline characteristics in the two groups were balanced (Table 1, and Table S2 in the Supplementary Appendix). The median age was 75 years, and patients were predominantly male.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tafamidis (N=264)	Placebo (N=177)
Age — yr		
Mean	74.5±7.2	74.1±6.7
Median (range)	75 (46–88)	74 (51–89)
Sex — no. (%)		
Male	241 (91.3)	157 (88.7)
Female	23 (8.7)	20 (11.3)
Race — no. (%)		
White	211 (79.9)	146 (82.5)
Black	37 (14.0)	26 (14.7)
Asian	13 (4.9)	5 (2.8)
Other	3 (1.1)	0
TTR genotype — no. (%)		
ATTRm	63 (23.9)	43 (24.3)
ATTRwt	201 (76.1)	134 (75.7)
Blood pressure — mm Hg		
Supine		
Systolic	115.4±15.4	115.1±15.7
Diastolic	70.4±10.3	70.2±9.5
Standing		
Systolic	115.5±15.5	115.9±15.9
Diastolic	70.6±9.9	71.0±10.3
Heart rate, mean — beats per minute		
Supine	70.7±12.3	69.9±11.7
Standing	72.9±12.9	73.8±12.2
NYHA Class — no. (%)		
Class I	24 (9.1)	13 (7.3)
Class II	162 (61.4)	101 (57.1)
Class III	78 (29.5)	63 (35.6)
Modified BMI†	1058.8±173.8	1066.4±194.4
NT-proBNP level — pg/ml		
Median	2995.9	3161.0
Interquartile range	1751.5–4861.5	1864.4–4825.0

* Plus-minus values are means ±SD. There were 264 patients in the tafamidis group and 177 patients in the placebo group in both the intention-to-treat and safety analyses. Percentages may not total 100 because of rounding. NT-proBNP denotes N-terminal pro-B-type natriuretic peptide, and NYHA New York Heart Association.

† The modified body-mass index (BMI) is calculated as the serum albumin level in grams per liter multiplied by the conventional BMI (the weight in kilograms divided by the square of the height in meters).



Among those who underwent randomization, 106 (24%) had ATTRm with Val122Ile, Thr60Ala, and Ile68Leu being the most common mutations. Predefined treatment adherence (taking $\geq 80\%$ of scheduled doses) was high, at 97.2% for tafamidis and 97.0% for placebo.

EFFICACY

In the primary analysis that hierarchically assessed all-cause mortality, followed by frequency of cardiovascular-related hospitalization, according to

analyses performed with the Finkelstein–Schoenfeld method, treatment with tafamidis was superior to placebo over 30 months ($P<0.001$). The win ratio²⁴ (number of pairs of treated-patient “wins” divided by number of pairs of placebo-patient “wins”) may be helpful in interpreting the Finkelstein–Schoenfeld result. The win ratio is 1.695 (95% confidence interval [CI], 1.255 to 2.289). According to Cox regression analysis, all-cause mortality was lower with tafamidis than with placebo (78 of 264 [29.5%] vs. 76 of 177

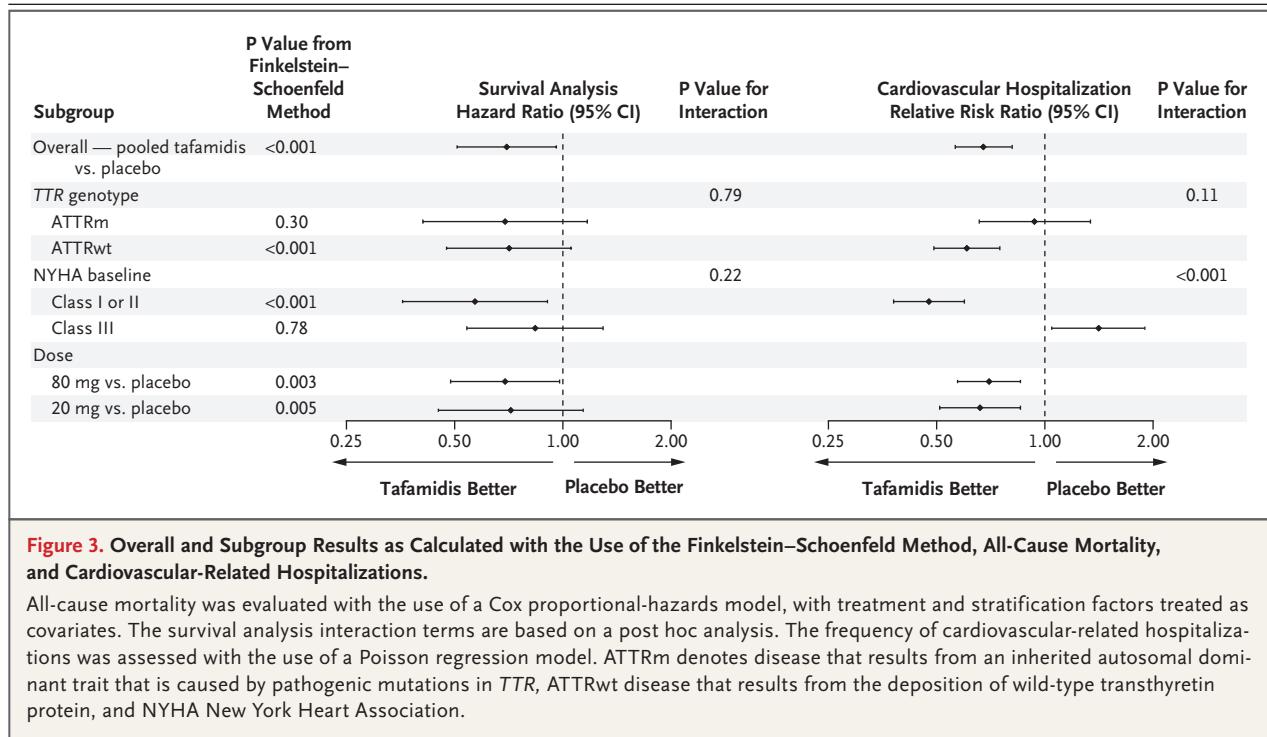


Figure 3. Overall and Subgroup Results as Calculated with the Use of the Finkelstein–Schoenfeld Method, All-Cause Mortality, and Cardiovascular-Related Hospitalizations.

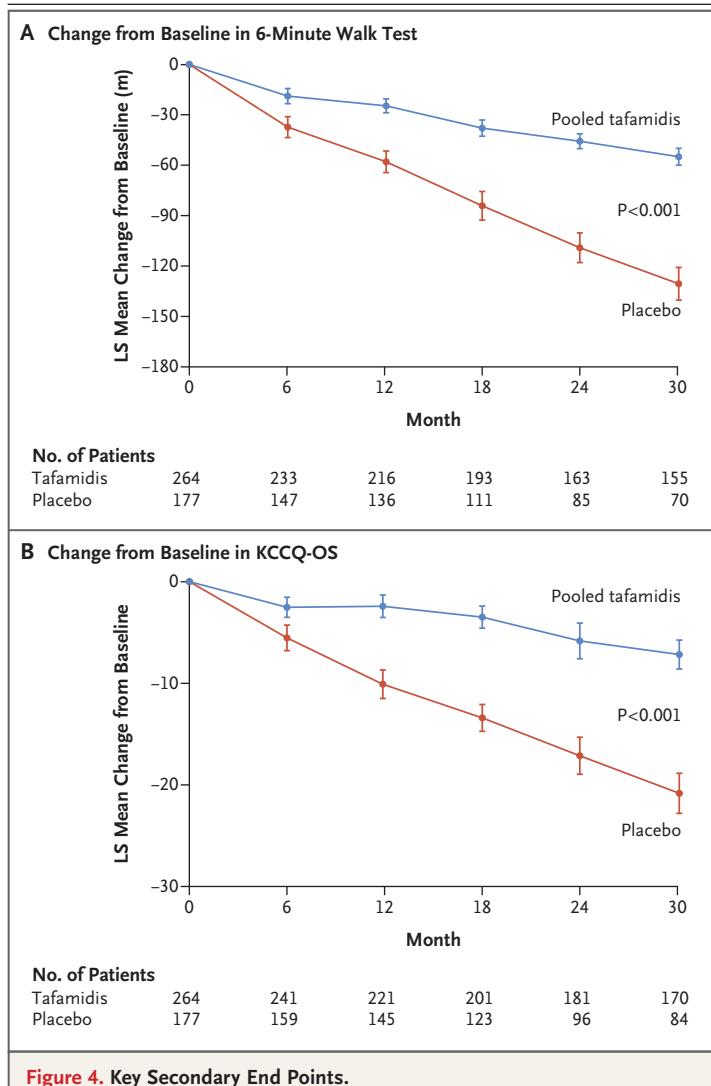
All-cause mortality was evaluated with the use of a Cox proportional-hazards model, with treatment and stratification factors treated as covariates. The survival analysis interaction terms are based on a post hoc analysis. The frequency of cardiovascular-related hospitalizations was assessed with the use of a Poisson regression model. ATTRm denotes disease that results from an inherited autosomal dominant trait that is caused by pathogenic mutations in *TTR*, ATTRwt disease that results from the deposition of wild-type transthyretin protein, and NYHA New York Heart Association.

[42.9%]; hazard ratio, 0.70; 95% CI, 0.51 to 0.96). According to the Poisson regression analysis, the rate of cardiovascular-related hospitalizations (0.48 vs. 0.70 hospitalizations per year; relative risk ratio, 0.68; 95% CI, 0.56 to 0.81) was lower with tafamidis than with placebo (see Table S3 in the Supplementary Appendix for post hoc negative binomial analysis). Kaplan–Meier survival curves showed that tafamidis resulted in a reduction in all-cause mortality, with the curves diverging after approximately 18 months of treatment (Fig. 2). Across prespecified subgroups, including those based on TTR status (ATTRwt vs. ATTRm), NYHA class (I or II vs. III), and tafamidis dose (80 mg vs. 20 mg), the difference in all-cause mortality and frequency of cardiovascular-related hospitalizations favored tafamidis over placebo, except in patients with NYHA class III disease at baseline, among whom the rates of cardiovascular-related hospitalizations were higher among patients receiving tafamidis than among those receiving placebo (Fig. 3). Using a prespecified Poisson-regression analysis, we observed an interaction between treatment and NYHA baseline classification. We did not observe an interaction between treatment and TTR status. A pre-specified sensitivity analysis of all-cause mortality

that did not treat transplantation involving heart transplantation or implantation of a cardiac mechanical assist device as death yielded a hazard ratio of 0.67 (95% CI, 0.49 to 0.94). An additional post hoc analysis of time to first cardiovascular-related hospitalization is provided (see Fig. S1 in the Supplementary Appendix).

Key secondary end points included the change from baseline to month 30 in the distance walked during the 6-minute walk test and in KCCQ-OS score. Tafamidis reduced the decline in the distance walked during the 6-minute test as compared with placebo (75.68 m [standard error, ± 9.24 ; $P < 0.001$]), with differences first observed at month 6 (Fig. 4A). Tafamidis also reduced the decline in the KCCQ-OS score as compared with placebo (13.65 [standard error, ± 2.13 ; $P < 0.001$]), with differences first observed at month 6 (Fig. 4B).

Exploratory end points included a smaller increase in the NT-proBNP level among patients receiving tafamidis than among those receiving placebo at months 12 and 30 (least-squares mean difference, -735.14 [95% CI, -1249.16 to -221.13] at 12 months and -2180.54 [95% CI, -3326.14 to -1034.95] at 30 months). Directionally positive echocardiographic findings (see Table S4 in the Supplementary Appendix), including a smaller de-

**Figure 4.** Key Secondary End Points.

Panel A shows the least-squares (LS) mean (\pm SE) change from baseline to month 30 in the distance walked in the 6-minute walk test in the pooled tafamidis group as compared with the placebo group. Panel B shows the LS mean (\pm SE) change from baseline for both groups in the Kansas City Cardiomyopathy Questionnaire—Overall Summary (KCCQ-OS) score, in which higher scores indicate better health status. I bars indicated standard errors.

crease in left ventricular stroke volume (least-squares mean difference, 6.28), were noted at month 30.

SAFETY AND ADVERSE EFFECTS

The safety profiles of tafamidis and placebo were similar. There was no meaningful difference in the safety of the two doses of tafamidis. Adverse events that emerged during treatment were gen-

erally mild to moderate in severity, and permanent discontinuation of tafamidis or placebo as a result of adverse events was less common in the tafamidis groups than in the placebo group (Table S5 in the Supplementary Appendix). Dose reduction related to adverse events were uncommon (two patients receiving tafamidis [0.8%] and four patients receiving placebo [2.3%]). The results of laboratory analyses related to safety did not differ between the tafamidis and placebo groups. Both diarrhea and urinary tract infections, adverse events previously reported in patients with familial amyloid polyneuropathy,²⁵ were less common in patients who received tafamidis than in those who received placebo. The most frequent adverse events are summarized in the Supplementary Appendix.

DISCUSSION

ATTR-ACT showed that tafamidis is superior to placebo in reducing the combination of all-cause mortality and cardiovascular-related hospitalizations. The evidence also supports the assertion that the risk of each component, when analyzed independently of the other, is reduced. Tafamidis was also associated with a significant reduction in the decline in functional capacity (as measured by the 6-minute walk test) and the decline in quality of life (as measured by the KCCQ-OS) at month 30, with differences first observed at 6 months. In contrast, the effect on overall survival emerged after approximately 18 months. This dissociation between the effect on symptoms and survival has also been observed with other therapies for systolic heart failure in which ventricular remodeling takes months to achieve.²⁶⁻²⁸

We observed a consistent benefit from tafamidis related to mortality across all subgroups. We also observed fewer cardiovascular-related hospitalizations among those who received tafamidis across all subgroups, with the exception of those with NYHA class III. We speculate that the higher hospitalization rate observed in this group is attributable to longer survival during a more severe period of disease, underscoring the importance of early diagnosis and treatment of this fatal, progressive disease, which can be difficult to diagnose.²⁹ Given the progressive nature of the disease and the mechanism through which tafamidis reduces amyloidogenesis — by specifically

stabilizing transthyretin tetramers — the drug is expected to have greater benefit when administered early in the disease course.³⁰

When the trial was designed, tissue biopsy was required for diagnosis, but an approach without biopsy — in which technetium-labeled bone scintigraphy tracing is used instead — has been validated as a method for the identification of patients. This approach is highly sensitive and specific for the diagnosis of transthyretin amyloid cardiomyopathy^{4,5,31} and can detect amyloid deposits before an increase in left ventricular wall thickness or the clinical syndrome of heart failure and a rise in cardiac biomarkers has occurred.^{32,33} This method can even predict prognosis.^{5,34} Early identification and treatment are now more likely given the availability of effective diagnostic tools and therapy.

Similarly, innovative methods are being developed and used for research in rare disease. In studies of rare disease such as transthyretin amyloid cardiomyopathy, small patient populations often limit recruitment and hinder the conduct of randomized trials. The Finkelstein–Schoenfeld method, used in this trial, is a validated technique that increases the sensitivity and power of the analysis of smaller cohorts and prioritizes the

importance of mortality while also addressing morbidity.

The overall incidence and type of adverse events were similar in the tafamidis and placebo groups. Discontinuation of the trial drug owing to adverse events that occurred during treatment was less common in patients who received tafamidis than in those who received placebo, and dose reductions were uncommon and occurred more often in the placebo group.

In conclusion, in patients with heart failure due to transthyretin amyloid cardiomyopathy, treatment with tafamidis reduced all-cause mortality and cardiovascular-related hospitalizations as compared with placebo. Tafamidis treatment also significantly reduced the decline in functional capacity and quality of life. These findings indicate that tafamidis is an effective therapy for patients with transthyretin amyloid cardiomyopathy.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

From the Columbia University Vagelos College of Physicians and Surgeons (M.S.M.) and Pfizer (J.H.S., A.I.B., P.H., J.S., M.B.S.), New York; Syneos Health, Raleigh, NC (B.G.); University College London and St. Bartholomew's Hospital, London (P.M.E.); the Amyloidosis Center, Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, and the University of Pavia, Pavia (G.M.), and the Department of Experimental, Diagnostic, and Specialty Medicine, University of Bologna, Bologna (C.R.) — both in Italy; the Amyloidosis Center (CEPARM), Federal University of Rio de Janeiro, Rio de Janeiro (M.W.C.); the Amyloidosis Center, Medical University of Heidelberg, Heidelberg, Germany (A.V.K.); the Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN (M.G.); Stanford University School of Medicine, Stanford, CA (R.W.); the French Referral Center for Cardiac Amyloidosis, Amyloidosis Mondor Network, GRC Amyloid Research Institute and Department of Cardiology, Assistance Publique–Hôpitaux de Paris, CHU Henri Mondor, and INSERM Unité 955, Clinical Investigation Center 006, and DHU ATVB, Creteil, France (T.D.); Penn Presbyterian Medical Center, University of Pennsylvania Health System, Philadelphia (B.M.D.); the Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago (S.J.S.); Cleveland Clinic, Cleveland (M.H.); the Medical University of South Carolina, Charleston (D.P.J.); and Pfizer, Groton, CT (T.A.P., S.R., M.S.).

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